Supplementary Appendix - Protocol

This appendix has been provided by the authors to give readers additional information about their work

Efficacy, Safety and Biomarker Analysis of Combined PD-L1 (Atezolizumab) and VEGF (Bevacizumab) Blockade in Advanced Malignant Peritoneal Mesothelioma

This supplement contains the following items:

1. Summary of Protocol Changes
2. Final protocol
3. Original protocol
4. Document comparison between final and original documents
5. Statistical analysis plan is included within the protocol body on page 76 in the final protocol and any changes are summarized and included in this document.

Summary of Protocol Changes

1. Modified RECIST inserted for measurement of disease response for pleural mesothelioma cohort.
2. Nasopharyngeal cohort removed EBV requirement (then closed).
3. HPV cohort included progression or intolerance to platinum-based chemotherapy, including oxaliplatin.
4. Merkel Cell Carcinoma cohort was transitioned to a post-immune-checkpoint inhibition cohort (then closed).
5. NET cohorts clarified to include precise terminology for grade 1 and 2 NET among varied primary sites and pathology reports.
6. Nephritis added to adverse event of special interests (AESIs) and specific management guidance added due to emerging data during the study.
7. Vasculitis, autoimmune hemolytic anemia, and severe immune skin reactions added to AESIs.
8. Grade 3 hypertension removed from the Bayesian toxicity monitoring rule to address error of omission in original protocol draft.

Final protocol

PROTOCOL

TITLE:	**A PHASE II, SINGLE-ARM OPEN-LABEL STUDY OF THE COMBINATION OF ATEZOLIZUMAB AND BEVACIZUMAB IN RARE SOLID TUMORS**
MD ANDERSON CANCER CENTER PROTOCOL NUMBER	2016-0861
GENENTECH PROTOCOL NUMBER:	ML39572
VERSION NUMBER:	12
VERSION DATE	3/11/2019
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	133805
INVESTIGATOR	Daniel M. Halperin, MD 1515 Holcombe Blvd Unit 426 Houston, TX 77030 Telephone: 713-792-2828 Fax: 713-745-1163 E-mail: dmhalperin@mdanderson.org
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab
MEDICAL MONITOR:	UT M.D. Anderson IND Office
SPONSOR:	UT M.D. Anderson
DATE FINAL:	See electronic date stamp below

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
LPLV	last patient, last visit
MTD	maximum tolerated dose
NCI	National Cancer Institute
NET	Neuroendocrine Tumor
ORR	objective response rate
PI	Principal investigator
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q3W	every 3 weeks
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
TC	tumor cell
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON THE SPECIFIC SOLID TUMORS BEING STUDIED

1.1.1 Appendiceal adenocarcinoma

Appendiceal tumors are rare, with an age-adjusted incidence of 0.12 cases per 1,000,000 per year.(McCusker et al., 2002) Metastatic appendiceal neoplasms are tumors characterized by a relatively indolent natural clinical course if low-grade and very aggressive biology if high grade.(Asare et al., 2016, Carr et al., 2016) Cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard therapy in low-grade tumors and results in prolonged survival, but is not effective in high grade tumors, where systemic therapy is the only option, but has limited benefit.(Smeenk et al., 2007) However, high tumor burden and medical comorbidities can exclude patients from curative intent surgery. Conventional cytotoxic chemotherapy in these patients has shown no or little clinical benefit.(Asare et al., 2016) There exists an unmet need for active targeted agents in this setting. Emerging data has shown a higher frequency of KRAS mutations in low-grade appendiceal neoplasms (70%-80%) compared to high-grade tumors.(Raghav et al., 2013, Alakus et al., 2014) Appendiceal adenocarcinomas mimic colorectal cancer to a large extent and are treated similarly. Immunotherapy has only been effective in microsatellite-unstable colorectal cancer, and novel strategies of immunomodulation are therefore needed in the treatment of cancers of the lower gastrointestinal tract.

1.1.2 Nasopharyngeal carcinoma

Approximately 3,200 cases of nasopharyngeal carcinoma (NPC) are diagnosed yearly in the USA. Unfortunately, there are no standard of care systemic treatments for patients with recurrent or metastatic NPC. Platinum-based chemotherapy is frequently used in the first line setting. In the second line and beyond, monotherapy regimens with gemcitabine, capecitabine, or docetaxel(Chua et al., 2003, Foo et al., 2002, Ngeow et al., 2011) are frequently used, with responses rates of approximately 30% and a median PFS of only 5 months.

NPC is an Epstein Barr Virus (EBV) driven malignancy. Chronic EBV infection leads to increased viral EBV load and expression of PD-1 on cytotoxic memory T-cells leading to T-cell exhaustion (Barber et al., 2006, Day et al., 2006). Increased PD-1 expression also occurs in the virally affected host cells. Latent EBV infection is also associated with expression of LMP-1 protein which induces PD-L1 expression (Fang et al., 2014). Increased PD-1 and PD-L1 work together to suppress the immune system, leading to decreased EBV cellular immunity. PD-L1 expression is almost universal in NPC (98% of cases) and clinical activity of PD-1 inhibitor single agent has been reported in a cohort of patients with refractory NPC [Hsu, ESMO 2015].

VEGF concentrations are substantially increased in patients with metastatic NPC(Qian et al., 2000). The higher expression of VEGF in EBV related tumors is related to higher rates of recurrence and shorter overall survival(Krishna et al., 2006). Bevacizumab given with

concurrent chemoradiation has been studied in NPC with promising results (Lee et al., 2012). VEGF suppresses the immune system and the combination of bevacizumab with checkpoint inhibitor has rendered encouraging results in metastatic melanoma (Hodi et al., 2014). Taken together, there is a strong rationale to study the anti-PD-L1/anti-VEGF combination in metastatic NPC, a highly unmet clinical need.

1.1.3 Human Papilloma Virus (HPV)-associated cancers

The human papilloma virus (HPV) is associated with the development of multiple malignancies including cervical, oropharyngeal, vulvar, vagina, penile, and anal cancer. In 2008, of the estimated 12.7 million cancers, 610,000 cases are believed to be attributed to HPV (Forman et al., 2012). It is estimated 89,000 patients will be diagnosed worldwide with the rare HPV associated cancers: vulvar, vagina, penile, and anal cancer [Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 2016- 02-25. [7/15/16]. The association of HPV has been well documented in both cervical and oropharyngeal cancer, as well. Each of these cancers has been linked to HPV in variable degrees: 90% of anal, cervical, and vaginal carcinomas; 70% of all vulvar cancers; and 50% of penile cancers. Currently, there is no standard treatment approach for patients with metastatic disease for these rare cancers, nor is there a standard of care for cervical cancer refractory to platinum-based chemotherapy. In short, clinical trial development has been lacking for these malignancies. Yet, there is a rising incidence of HPV associated cancers, notably anal and oropharyngeal cancers (www.seer.gov). Identification of treatment options for the HPV associated malignancies of metastatic or surgically unresectable anal, penile, and vaginal, vulvar, and refractory cervical cancer, is clearly an unmet need. Intriguingly, treatment with the immune checkpoint inhibitor, nivolumab, in refractory metastatic squamous cell carcinoma of the anal canal (NCI9673) yielded initial proof of concept of the activity of immunotherapy against an HPV-associated malignancy, with an overall response rate of 24% (CR rate of 5%; PR rate of 19%) [Morris et al., ASCO 2016].

1.1.4 Merkel Cell Carcinoma

Merkel Cell Carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, with an estimate incidence of 1,500 new cases per year in the US, which is rising. Patients with metastatic disease have a 2-year survival of approximately 25%, representing a major unmet clinical need (Lemos et al., 2010). Currently, there is no FDA approved treatment for unresectable, recurrent, or metastatic MCC. Given it is a high-grade neuroendocrine carcinoma, patients are usually treated with chemotherapy regimens frequently used in small cell lung cancer [NCCN guidelines], however, responses are of short duration and the benefit of chemotherapy is questionable. MCC is associated with the Merkel cell polyomavirus in 40-100% of the cases (Feng et al., 2008, Rollison et al., 2010). The risk of developing MCC is increased from 5 to 50-fold in immunocompromised individuals, and there are reports of tumor regression following improvement in immune system

function(Bhatia et al., 2011). PD-L1 expression is seen in 49% of MCC and expression in tumor-infiltrating lymphocytes occurs in 55% of the patients (Lipson et al., 2013). Recently, encouraging activity has been reported with single agent anti-PD1 in this patient population (Nghiem et al., 2016). VEGF-A, VEGF-C and VEGFR2 overexpression is also prevalent in MCC and correlates with metastatic potential (Brunner et al., 2008, Kukko et al., 2007). Thus, there is significant rationale for pursuing dual VEGF and PD-L1 blockade.

1.1.5 Neuroendocrine tumors, pancreatic and extra pancreatic

Well-differentiated neuroendocrine tumors (NETs) are relatively rare malignancies of a diffuse neuroendocrine network with a variable clinical course, and median survival ranging from 24 months to over ten years(Yao et al., 2008). Because of differences in effective therapy, they are often classified as either pancreatic NETs (pNETs) or extra pancreatic NETs. The mTOR inhibitor everolimus and the somatostatin analogues lanreotide and octreotide are the only drugs approved for the oncologic management of gastrointestinal NETs (Caplin et al., 2014, Rinke et al., 2009). In contrast, chemotherapy is standard in pancreatic NETs (PNETs) (Moertel et al., 1980, Moertel et al., 1992, Kouvaraki et al., 2004), as is the somatostatin analogue lanreotide (Caplin et al., 2014) and targeted agents such as everolimus(Yao et al., 2010) and sunitinib (Raymond et al., 2011). pNETs remain life-limiting, and response rates are universally less than 10%. Additional therapies are therefore desperately lacking for NETs. Immunotherapy, such as with interferon, as well as anti-VEGF therapy with bevacizumab and sunitinib, have been investigational and standard therapies in the NET field for decades, but the two strategies have never been tested in combination.

1.1.6 Peritoneal mesothelioma

Malignant peritoneal mesothelioma (MPM) is a rare disease and constitutes about 10% of all cases of malignant mesothelioma.(Rodriguez et al., 2009) With an annual incidence of 1 per 100,000 population, approximately 300 – 400 cases are diagnosed in the United States every year.(Rodriguez et al., 2009) Current options for systemic therapy are limited and afford modest survival benefit.(Janne et al., 2005, Vogelzang et al., 2003) The standard of care for frontline unresectable MPM is platinum-pemetrexed.(Vogelzang et al., 2003, Janne et al., 2005) Beyond the first-line therapy, no good standard of care or FDA approved agents exist. Single agent gemcitabine and vinorelbine are used in the salvage setting due to modest activity seen in pleural mesothelioma (response rate 8-16%) and are riddled with toxicity.(van Meerbeeck et al., 1999, Stebbing et al., 2009) Historically, the progression-free survival (PFS) in this setting is about 1.7 months (Stebbing et al., 2009, van Meerbeeck et al., 1999) Therefore, there is an unmet and critical need to develop novel agents for this orphan disease. Tremelimumab, a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA4), has shown encouraging clinical activity and acceptable safety profile in refractory patients with malignant pleural mesothelioma with a disease control rate of 30% and a PFS of 6.2 months.(Calabro et al., 2013) The preliminary results of KEYNOTE-028 trial with a cohort of patients (N = 25) with malignant pleural mesothelioma (AACR 2015) showed an ORR of 28% and SD in 48% patients.(Karim and

Leighl, 2016) One of our patients with MPM treated with Atezo on protocol 2015-0239, who was refractory to cisplatin and pemetrexed received a major response at first restaging. Addition of bevacizumab to chemotherapy significantly improves OS in malignant mesothelioma and is currently being considered for regulatory approval (Zalcman et al., 2016). Furthermore, VEGF leads to a functional defect of the dendritic cells and decreased antigen presentation and inhibition with bevacizumab increases B and T cell compartments (Manzoni et al., 2010). Therefore combining two potentially active therapies with plausible synergistic effects could help antitumor efficacy of this combination in mesothelioma.

1.1.7 Pleural mesothelioma

Malignant mesothelioma (MM) is an orphan disease that is difficult to treat.(Tsao et al., 2009) Novel agents are critically needed as the median overall survival with advanced MM is 1 year and there are no FDA approved agents in the salvage setting. In the past year, The Intergroupe Francophone de Cancerologie Thoracique (IFCT) published their positive results on the Phase III MAPS trial which compared cisplatin-pemetrexed with and without bevacizumab. Both the PFS (HR 0.61, p<0.0001) and OS (HR 0.77, p=0.0167) were prolonged in the patients who received bevacizumab (Zalcman et al., 2015). This is the first triplet regimen with a novel biologic agent that has demonstrated a clear survival benefit to MM patients, and is undergoing evaluation for regulatory approval.

Programmed death 1 (PD1) protein, a T-cell co-inhibitory receptor, and one of its ligands PD-L1 are targets for immunotherapy. PD-1 receptor binds with PD-L1 and inhibits T-cell inhibition and downregulates T-cell responses. Inhibition of their interaction has been shown to lead to restoration of T-cell activity and a subsequent anti-tumor effect in several tumor types. There are several PD-L1 inhibitors under development; to name a few, BMS0936559 (Bristol-Meyers Squibb), MEDI-4736 (Medimmune), and atezolizumab (Genentech) (Brahmer et al., 2012, Brahmer et al., 2014, Davies, 2014). In non-small cell lung cancer, response rates ranging from 10% to 26% have been reported using these PD-L1 inhibitors as monotherapy in Phase I and II trials (Brahmer et al., 2014, Brahmer, 2013, Brahmer et al., 2012, Davies, 2014). MM is anticipated to be a highly immunogenic disease (Thomas and Hassan, 2012). At ESMO 2014, Mansfield et al. (Mansfield et al., 2014) reported a 40% PD-L1 IHC expression in pleural mesotheliomas (n=224) using a mouse monoclonal anti-human B7-H1 (clone 5H1-A3). PD-L1 IHC expression was associated with more disease burden and less offers of surgery to the patient. Also, PD-L1 IHC expression was associated with a worse survival 6 months vs 14 months, p<0.0001) (Mansfield et al., 2014). At AACR 2015, pembrolizumab was shown in 25 mesothelioma patients to have an overall response rate of 28% and 48% stable disease for a disease control rate of 76%. There were no new safety signals with this regimen.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also

known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al., 2016, Rosenberg et al., 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma or non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 BACKGROUND ON BEVACIZUMAB

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 22,000 patients and in multiple tumor types. Approximately 1,720,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab’s safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.66 ($p < 0.001$) and a median survival of 20.3 vs. 15.6 months. Similar increases were seen in progression-free survival (10.6 vs. 6.2 months; HR 0.54, $p < 0.001$), overall response rate (34.8% vs. 44.8%; $p = 0.004$) and duration of response (10.4 vs. 7.1 months; HR 0.62, $p = 0.001$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, November 2012). Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5 FU−based chemotherapy for subjects with metastatic colorectal cancer.

Bevacizumab has also been approved based on additional Phase III trials in metastatic CRC (E3200 and ML18147) non−small cell lung cancer (NSCLC; E4599), and renal cell

carcinoma (RCC; AVOREN) which also demonstrated clinical benefit from bevacizumab. Furthermore, Phase II studies in glioblastoma (GBM; AVF3708g and NCI-06-C0064) showed an improvement in objective response rate. These studies led to accelerated approval by the FDA for recurrent GBM.

In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated, Avastin naive metastatic CRC patients. In Study ML18147, bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy regimens demonstrated a statistically significant increase in OS compared to oxaliplatin- or irinotecan-based chemotherapy alone (11.2 vs. 9.8 months, respectively, HR = 0.81; p=0.0062) in metastatic CRC patients who had previously received bevacizumab as a part of their 1st line treatment (Bennouna et al., 2013). These two studies led to FDA approvals for bevacizumab for previously treated metastatic CRC patients, in 2006 and 2013, respectively.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; p = 0.003). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006.

In previously untreated metastatic RCC patients, bevacizumab in combination with interferon-alfa showed an improved progression free survival compared to interferon-alfa alone (10.2 vs. 5.4 months, respectively; HR=0.63; p=0.0001). These results supported the FDA approval of bevacizumab with interferon-alfa in metastatic RCC in July 2009.

Two Phase II trials investigated bevacizumab as a single agent in patients with recurrent GBM. In AVF3708g, patients with recurrent GBM were randomized to bevacizumab or bevacizumab plus irinotecan and demonstrated an improvement in objective response rate (28.2% vs. 37.8%, respectively). The NCI-06-C0064 study was single arm Phase II study in recurrent GBM patients treated with bevacizumab alone and showed an objective response rate of 19.6%. This study supported the results from AVF3708g, and based on the objective response rate in these two trials, the FDA granted accelerated approval for bevacizumab as a single agent in GBM patients with progressive disease following prior therapy. In 2013, results from two phase III randomized controlled trials for newly diagnosed GBM were presented, one Roche-sponsored trial (AVAglio) and one cooperative group trial (RTOG 0825). In AVAglio, progression free survival was significantly longer with bevacizumab when added to radiation therapy/temozolomide (HR 0.64, mPFS 10.6 vs 6.2 months). Health-related quality of life (HRQoL) and Karnofsky performance score (KPS) were stable/improved during PFS (both arms). Patients receiving bevacizumab plus radiation therapy/temozolomide had diminished corticosteroid requirement, but reported more adverse events (AEs) compared with placebo plus

radiation therapy/temozolomide (serious AEs: 36.6% vs 25.7%; grade ≥3: 62.7% vs 50.1%; grade ≥3 AEs of special interest to bevacizumab: 28.7% vs 15.2%). In RTOG 0825, PFS was extended for bevacizumab (7.3 vs.10.7 months, HR 0.79) but did not meet the pre-specified endpoint for significance. There was no difference between arms for overall survival (median 16.1 vs.15.7 months, HR 1.13).

Lastly, in the E2100 study, patients with untreated metastatic breast cancer who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively, HR 0.48; $p<0.0001$) and this led to the accelerated approval of bevacizumab in metastatic breast cancer. Unfortunately, the clinical benefit was not confirmed in subsequent trials and the FDA ultimately removed the label for the breast cancer indication. (See the Bevacizumab Investigator Brochure for additional details).

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite recent advances in the treatment of more common cancers, patients with rare solid tumors have seen slow progress in recent years. For the reasons specified in Section 1.1, each of the tumor types being investigated in this study has strong preclinical and/or clinical rationale for a study of checkpoint inhibition in combination with VEGF inhibition, and presents an unmet medical need in the metastatic setting. It is therefore imperative to explore the antitumor activity of this combination in these cohorts.

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Chen et al., 2012, Hodi et al., 2010, Kantoff et al., 2010).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al., 2005, Keir et al., 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer,

breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

In multiple murine tumor models, the interruption of the interaction between PD-L1 and PD-1 resulted in anti-tumor effects (Iwai et al. 2002; Strome et al. 2003). PD-L1 blockade in the syngeneic colorectal cancer model MC-38 (expressing the foreign antigen ovalbumin) resulted in complete responses in all test animals in fewer than 2 weeks of treatment (unpublished Roche data).

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. VEGF is believed to be involved in immune response via the induction of myeloid-derived suppressor cells (MDSCs). These VEGF-induced MDSCs can suppress both T-cell and dendritic-cell function (Gabrilovich 2012). Anti-VEGF therapies may elicit immune responses through diverse mechanisms, including increased trafficking of T cells into tumors (Manning et al. 2007; Shrimali et al. 2010), reduced frequency of MDSC (Kusmartsev et al. 2008), reduction of suppressive cytokines and tumor-infiltrating T regulatory cells and MDSCs (Roland et al. 2009), and increased CD8+ and CD4+ central memory T cells (Hodi et al. 2011).

Collectively, the role of VEGF in the immune response and its critical role in the pathogenesis of multiple malignancies, including several of those in this study, provide a compelling rationale to test whether inhibition of the PD-L1/PD-1 pathway with a human anti−PD-L1 IgG1 effector less antibody with anti-VEGF therapies will result in improved clinical benefit for patients with these diseases.

The safety profile and associated benefit and risk of atezolizumab as a single agent (Phase Ia Study PCD4989g) and in combination with bevacizumab (Phase Ib Study GP28328 and Phase II Study WO29074) support its continued development. In the Phase Ib study of atezolizumab + bevacizumab (Study GP28328), 1 treatment-related grade 3-5 adverse event was observed (Table 1), and the most commonly observed AEs were fatigue, nausea, and pyrexia (Table 2).

Table 1 All Reported Adverse Events in Bevacizumab + Atezolizumab Arm of Study GP28328

Parameter	No (%) of Adverse Events			
	Total		Treatment-Related	
Any adverse event	35	(100.0)	27	(77.1)
Grade 3-5 adverse event	18	(51.4)	1	(2.9)

Serious adverse event	14	(40.0)	0	(0.0)
Adverse event leading to death (Grade 5)	1	(2.9)	0	(0.0)

Table 2 Reported Adverse Events in at least 10% of Patients in Bevacizumab + Atezolizumab Arm of Study GP28328

	No (%) of Adverse Events			
Preferred Term	Total		Treatment-Related	
Any adverse event	35	(100.0)	27	(77.1)
Fatigue	16	(45.7)	7	(20.0)
Nausea	13	(37.1)	7	(20.0)
Pyrexia	13	(37.1)	6	(17.1)
Diarrhea	11	(31.4)	8	(22.9)
Decreased appetite	9	(25.7)	5	(14.3)
Abdominal pain	7	(20)	0	(0.0)
Chills	7	(20.0)	4	(11.4)
Hypertension	7	(20.0)	0	(0.0)
Vomiting	7	(20.0)	2	(5.7)
Cough	6	(17.1)	3	(8.6)
Dyspnoea	6	(17.1)	2	(5.7)
Oedema peripheral	6	(17.1)	0	(0.0)
Upper respiratory tract infection	6	(17.1)	0	(0.0)
Anaemia	5	(14.3)	2	(5.7)
Anxiety	5	(14.3)	0	(0.0)
Epistaxis	5	(14.3)	1	(2.9)

Headache	5 (14.3)	0 (0.0)
Pain in extremity	5 (14.3)	1 (2.9)
Pneumonia	5 (14.3)	0 (0.0)
Pruritus	5 (14.3)	3 (8.6)
Rash	5 (14.3)	3 (8.6)
Arthralgia	4 (11.4)	1 (2.9)
Constipation	4 (11.4)	0 (0.0)
Insomnia	4 (11.4)	0 (0.0)
Productive cough	4 (11.4)	0 (0.0)
Bone pain	3 (8.6)	2 (5.7)
Musculoskeletal pain	3 (8.6)	1 (2.9)

This trial will enroll patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with bevacizumab is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab when given in combination with bevacizumab (atezo + bev) in patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. Specific objectives and corresponding endpoints for the study are outlined below.

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezo + bev	• Objective response (defined as a complete response or partial response on two consecutive occasions ≥ 4

	weeks apart) as determined by a blinded independent radiologist according to RECIST v1.1 (modified RECIST for pleural mesothelioma)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of atezo + bev	• Objective response as determined by an independent radiologist according to immune-modified RECIST • PFS (defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first) as determined by an independent radiologist according to RECIST v1.1 (modified RECIST for pleural mesothelioma). • DOR (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first) as determined by an independent radiologist according to RECIST v1.1 (modified RECIST for pleural mesothelioma) • Disease control as determined by the independent radiology according to RECIST v1.1 (modified RECIST for pleural mesothelioma) • Overall survival, defined as the time from enrollment to death from any cause • PFS as determined by an independent radiologist according to immune-modified RECIST • DoR as determined by an independent radiologist according to immune-modified RECIST • Disease control as determined by the independent radiologist according to immune-modified RECIST
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of atezo + bev	• Occurrence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to atezo + bev (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to atezo + bev, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, or can increase the	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

knowledge and understanding of disease biology	

DOR = duration of response; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

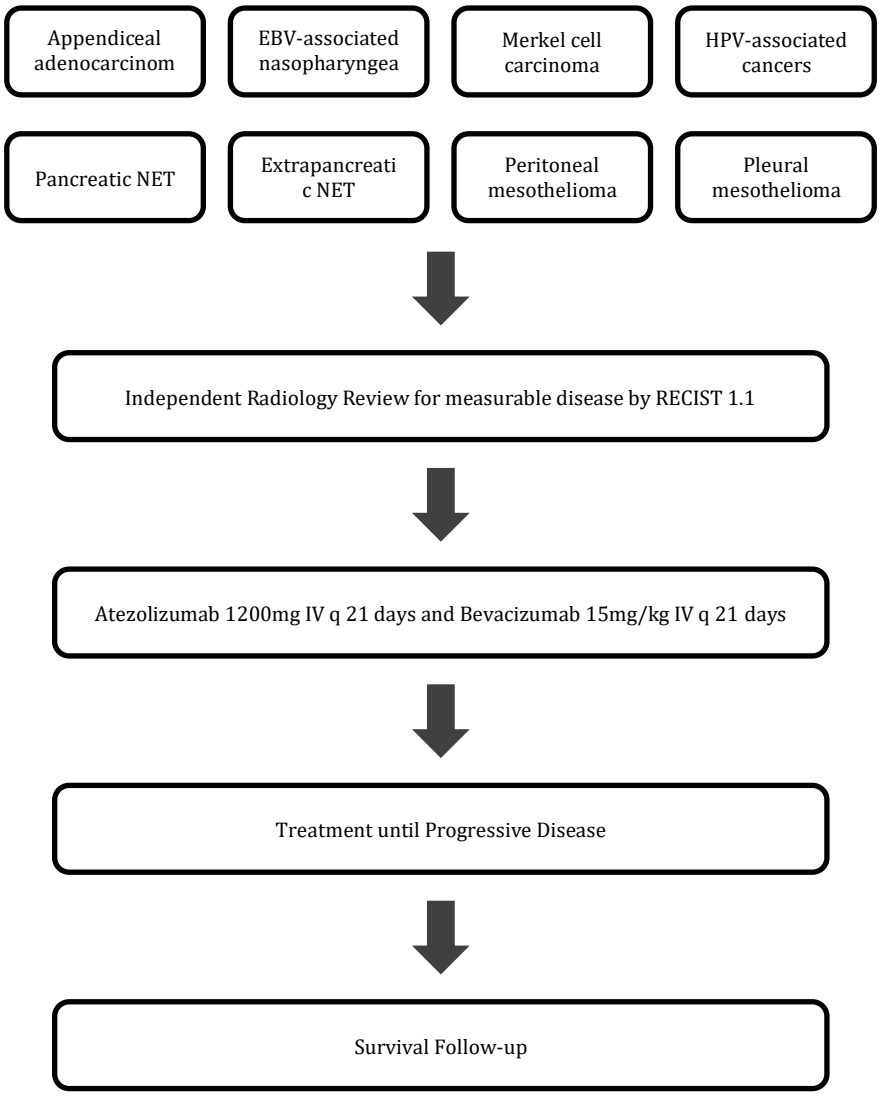
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This study will be a Phase II, single-center, single-arm, open label study evaluating the efficacy and safety of the combination of bevacizumab and atezolizumab in parallel cohorts of patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. The study will enroll approximately 160 patients, with 20 patients in each cohort.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV = intravenous; RECIST = Response Evaluation Criteria in Solid Tumors.

Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle and bevacizumab will be administered by intravenous (IV) infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1(modified RECIST for pleural mesothelioma) may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients

who meet criteria for disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) while receiving atezolizumab will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients will undergo tumor assessments by independent radiology review at scheduled intervals during the study (see Section 4.5.5 and Appendix 1 for details).

The expected total length of time on study is anticipated to be approximately 15 months, with 2 weeks spent in screening, 4 weeks in washout, 12 months receiving therapy, and 2 months of follow-up prior to the final protocol visit.

Patients will undergo mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by the investigator, on cycle 2 days 1 and at the time of first evidence of radiographic disease progression according to RECIST v1.1 (modified RECIST for pleural mesothelioma) within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner. These samples will be analyzed to evaluate tumor-infiltrating immune cells [ICs]). In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, which is expected to be 2 months after the last dose of either agent is administered, given that both atezolizumab and bevacizumab have elimination half-lives of approximately 28 and 21 days, respectively. The end of the study is expected to occur approximately 14 months after the last patient is enrolled. In addition, the PI may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Primary and Secondary Endpoints

The primary endpoint of the study is objective response using RECIST 1.1 (modified RECIST for pleural mesothelioma). Each cohort will be assessed independently, given that each individual disease under study has a distinct natural history. Objective response has long been a standard endpoint in phase II studies seeking preliminary evidence of anti-tumor efficacy, and has been identified as predictive of phase III outcome across tumor types (Oxnard et al., 2016). In pleural mesothelioma, modified RECIST has become standard due to improved quantification of disease burden in the context of a disease more prone to growing along the pleural surface rather than in discrete spheroids.

Secondary endpoints of PFS and OS are accepted assessments of treatment benefit across patient populations, and PFS will be measured using both RECIST 1.1 (modified RECIST for pleural mesothelioma) and irRECIST to permit both accurate reflection of immunotherapy activity and comparison to prior studies.

3.3.2 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) Q3W was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration–to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose. Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg).

3.3.3 Rationale for Patient Population

This study will enroll patients with advanced appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extra pancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma, regardless of PD-L1 expression.

Each of these advanced cancers remains incurable and life limiting. For nearly all of these tumor types, there is no FDA-approved therapy for the patient population being included in the study. The major exceptions are the neuroendocrine tumor cohorts, where FDA-approved therapy is available, but is frequently deferred in favor of clinical trials of promising agents in appropriately selected patients, given the overall need for additional therapies. Therefore, there remains a continuing need for more efficacious, safe, and better-tolerated treatments for patients with these rare cancers. As discussed in section 1.1, each tumor type has strong preclinical and/or clinical rationale for studying combined PD-L1 and VEGF inhibition to match the unmet need for additional therapies.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 correlates with response to therapy in several, but not all tumor types (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016).

Atezolizumab monotherapy has demonstrated clinical efficacy and is generally well tolerated in patients with other malignancies (Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016). In a Phase II study (GO28753), patients with advanced NSCLC had a significant improvement in OS when treated with atezolizumab compared with docetaxel in the second- or third-line setting (Fehrenbacher et al. 2016).

3.3.4 Rationale for Evaluating Atezolizumab in these Patient Populations

Immune checkpoint inhibitors, including atezolizumab, have demonstrated the potential to deliver significant clinical benefit to patients with advanced cancer (see Section 1.2). In this respect, atezolizumab is an example of an agent that is well tolerated and has the potential to deliver an excellent therapeutic index. In addition, because these therapies have the potential to induce potent anti-tumor immunity, there exists the potential for long-term durable responses.

Each of the diseases under study has significant rationale for studying the impact of immunomodulation. In appendiceal adenocarcinoma, the significant genomic, morphologic, and immunologic similarities to colorectal adenocarcinoma, in which this combination has already shown promise in study GP28328 (NCT01633970). In EBV-associated nasopharyngeal carcinoma, PD-L1 expression and VEGF overexpression are nearly universal, with PD-L1 suppressing the response to EBV (Barber et al., 2006, Fang et al., 2014). PD-1/PD-L1 inhibition has already shown promise in treating HPV-associated squamous cell carcinoma of the anal canal (Morris et al., ASCO 2016), Merkel

cell carcinoma (Nghiem et al., 2016), and mesothelioma (Karim and Leighl, 2016). In neuroendocrine tumors, VEGF inhibition and immunomodulation have both played important roles in the treatment of advanced disease, but the two strategies have never been combined.

3.3.5 Rationale for Evaluating Atezolizumab and Bevacizumab in combination

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggest that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune-cell recruitment to the tumor site (Bouzin et al. 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study of melanoma patients combining an immunomodulatory antibody (anti−CTLA-4; ipilimumab) and bevacizumab (Hodi et al. 2011). In this study of an immunomodulatory agent and bevacizumab, best overall responses were PR in 8 of 22 patients (35%) and stable disease in 6 of 22 patients (27%). All responses were durable for > 6 months. Therefore, the combined treatment with atezolizumab and bevacizumab may augment the antitumor immune response, resulting in improved and more durable clinical benefit.

3.3.6 Rationale for Open-Label Study

An open-label study design was chosen for this trial for a number of reasons. Given the known toxicities associated with immunotherapy, patients assigned to atezolizumab-containing arms, as well as physicians, may be capable of identifying treatment assignment in a blinded study. In addition, a blinded study would require prolonged administration of placebo, which could pose a significant burden to patients. Furthermore, because of the potential for pseudoprogression in patients randomized to atezolizumab-containing arms, a blinded study would require all patients to continue treatment until loss of clinical benefit regardless of whether they were receiving atezolizumab. This could then delay subsequent treatment with approved therapies in patients assigned to the control arm, as well as increase the complexity of treatment decisions.

To ensure the validity of data collected in an open-label study, efficacy analyses will include a supportive analysis based on IRF assessment of progression. In addition, the strategy and timing for final analysis of the primary endpoint, including censoring rules and methods for handling missing data, have been pre-specified in the protocol.

3.3.7 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients to continue treatment after apparent radiographic progression per RECIST v1.1 (modified RECIST for pleural mesothelioma), provided the benefit-risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.1). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status.

3.3.8 Rationale for the Use of Immune-Modified RECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix 4). It is required that radiographic progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression (caused by immune cell infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, use of immune-modified RECIST will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit.

3.3.9 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, after 3 weeks of therapy and at the time of first evidence of radiographic disease progression to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by immune cell infiltration) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T-cell activation, circulating tumor DNA (ctDNA) concentration, and lymphocyte subpopulations may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible, tumor tissue collected at 3 weeks of therapy and at the time of progression will enable NGS and RNA profiling to identify germline and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 160 patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extra pancreatic neuroendocrine tumors, peritoneal mesothelioma, and peritoneal mesothelioma (20 patients per diagnosis) will be enrolled in this study.

4.1.1 Inclusion Criteria

4.1.1.1 Basket-specific Inclusion Criteria

1. Appendiceal adenocarcinoma
    a. Metastatic appendiceal adenocarcinoma
    b. Not considered candidate for curative surgery

2. Nasopharyngeal carcinoma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Any number of prior therapies, including 0

3. Human Papilloma Virus-associated cancers
    a. Histologically proven squamous carcinoma of the anal canal, penile, vaginal, vulva, or cervical cancer with progression or intolerance to at least one treatment regimen including cisplatin, oxaliplatin or carboplatin will be enrolled. HPV confirmation is not required.
    b. Patients must have metastatic disease not amenable to surgical resection.
    c. If HIV+ positive, all patients infected with Human Immunodeficiency Virus (HIV) and CD4+ T cell count > 400 cells/mm^3 may be eligible for study.
    d. Patients co-infected with hepatitis B virus and/or hepatitis C virus may be included in this study provided that their liver function tests remain within the limits listed above. Patients must be followed by a hepatologist during the course of this study.

4. Merkel Cell Carcinoma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
    c. Any number of prior therapies

5. Neuroendocrine tumors, pancreatic
    a. Grade 1 or grade 2 (or described as low grade, intermediate grade, well differentiated, or moderately differentiated) according to reviewing pathologist
    b. Progressive disease over the preceding 12 months
    c. Any number of prior therapies, including 0
    d. Patients using a somatostatin analogue for symptom control must be on stable doses for 56 days prior to enrollment.

6. Neuroendocrine tumors, extra pancreatic
    a. Grade 1 or grade 2 (or described as low grade, intermediate grade, well differentiated, or moderately differentiated; typical or atypical carcinoid if originating in lung) according to reviewing pathologist
    b. Progressive disease over the preceding 12 months
    c. Any number of prior therapies, including 0
    d. Patients using a somatostatin analogue for symptom control must be on stable doses for 56 days prior to enrollment.

7. Peritoneal mesothelioma
    a. Refractory or intolerant to platinum and pemetrexed systemic therapy
    b. Not considered candidate for curative surgery

8. Pleural mesothelioma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Refractory to platinum and pemetrexed systemic therapy
    c. Any number of prior therapies

4.1.1.2 General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

  The pleural mesothelioma cohort will require measurable disease according to modified RECIST as specified in the Appendix 5.
- ECOG Performance Status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L without transfusion
  - WBC Count $\geq$ 2500/ul
  - Hemoglobin ≥ 90 g/L

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN
  - Serum albumin ≥ 2.5 g/dL
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the last dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea

with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Basket-specific Exclusion Criteria

1. Appendiceal adenocarcinoma
    a. Complete or partial bowel obstruction
2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
    a. none
3. Human Papilloma Virus-associated cancers
    a. None
4. Merkel Cell Carcinoma
    a. none
4. Neuroendocrine tumors, pancreatic
    a. Grade 3, poorly differentiated neuroendocrine carcinoma
    b. Large cell or small cell histology
5. Neuroendocrine tumors, extrapancreatic
    a. Grade 3, poorly differentiated neuroendocrine carcinoma
    b. Large cell or small cell histology
6. Peritoneal mesothelioma
    a. None
7. Pleural mesothelioma
    a. None

4.1.2.2 General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment for the studied cancer within 28 days prior to initiation of study treatment}
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the bevacizumab formulation

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $<$ 10% of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Positive HIV test at screening (except in cohort 3, HPV-associated cancers)
- Except in cohort 3, HPV-associated cancers, active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test and negative HBV DNA test at screening, are eligible for the study.

- Except in cohort 3, HPV-associated cancers active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study, or up to 5 months following the anticipated last dose of atezolizumab.
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Except for cohort 4, Merkel cell carcinoma, prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

  Patients who received low-dose immunosuppressant medication are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg).

  Anti-hypertensive therapy to maintain a systolic blood pressure <150 mmHg and/or

diastolic blood pressure < 100 mmHg is permitted.

- Prior history of hypertensive crisis or hypertensive encephalopathy
- History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
- Patients with a baseline ECG demonstrating a QTc > 460 ms
- Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 calendar days prior to Cycle 1, Day 1) use of dipyramidole, ticlopidine, clopidogrel, or cilostazol.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
- Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection

  All patients with $\geqslant$ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Treatment with the combination of atezolizumab and bevacizumab will be administered to all patients in an open-label, unblinded fashion. Patients will be assigned to cohorts based on tumor histology as assessed by an MD Anderson Cancer Center pathologist.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

Atezolizumab will be supplied by Genentech Inc as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

Atezolizumab may be prepared, handled, and administered per the current FDA-approved package insert.

4.3.1.2 Bevacizumab

Bevacizumab will be supplied by the Genentech Inc of Basel, Switzerland as a clear-to-slightly-opalescent, sterile liquid ready for parenteral administration. Each 400-mg (25-mg/mL) glass vial contains 16 mL of bevacizumab (25 mg/mL) with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only. For further details, see the Bevacizumab Investigator's Brochure.

Bevacizumab is intended for use solely in clinical trials. The drug provided for clinical trial use is expected to be very similar in safety and activity to the commercially marketed drug (Avastin®).

Bevacizumab may be prepared, handled, and administered per the current FDA-approved package insert.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of any of the study treatments should be noted on the electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Atezolizumab will be administered prior to bevacizumab, with a minimum of 5 minutes between dosing.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±5) minutes after the infusion.

Refer to the FDA-approved package inserts for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.3 and in the Atezolizumab Investigator's Brochure.

4.3.2.2 Bevacizumab

The dose of bevacizumab in this study is 15 mg/kg administered by IV infusion every 3 weeks on Day 1 each 21-day cycle. The interval between infusions must not be < 10 days. The bevacizumab dose will be based on the patient’s weight at enrollment and will remain the same throughout the study unless there is a weight change of > 10% from baseline. It is not necessary to correct dosing based on ideal weight, unless warranted per institutional guidelines/standard.

The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The patient should be

observed for at least 2 hours after the first administration of the combination and for 1 hour (± 30 minutes) for subsequent infusions.

If a patient experiences an infusion-associated adverse event, he or she may be pre-medicated for the next bevacizumab infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes as long as the patient continues to be pre-medicated. If a patient experiences a second episode of an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 (± 15) minutes. Similarly, if a patient experiences a second episode of an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 (± 10) minutes.

Upon receipt of the bevacizumab, vials are to be refrigerated at 2°C−8°C (36°F−46°F) and should remain refrigerated until use. Vials should be protected from light. DO NOT FREEZE. DO NOT SHAKE. VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab and bevacizumab) will be provided by the Genentech Inc where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Genentech Inc with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Genentech Inc. The site must obtain written authorization from the Genentech Inc before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded in the electronic medical record.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 7).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, except as outlined below.

  After Cycle 1, Day 14, palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and bevacizumab may be continued during palliative radiotherapy.

  Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Re-screening is required if a patient has not met all of the eligibility criteria within 28 days from the original date of the screening visit. Re-screening refers to repeating the entire screening process with the exception of performing a repeat biopsy to collect a tumor tissue sample to be used to determine PD-L1 status and repeating CT and/or MRI imaging scans used for tumor assessment, provided the biopsy tissue sample and imaging scans were obtained during the original screening visit. Patients are only allowed to be re-screened twice. Blood samples may be redrawn due to sample handling problems, breakage, or sample integrity, without being considered a re-screen.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the

cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Height will be assessed at baseline, and weight will be assessed at each study visit.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and every 9-12 (± 1) weeks thereafter (with neuroendocrine cohorts 5 and 6 assessed every 12 weeks and all other cohorts assessed every 9 weeks), regardless of dose delays, until radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) or (for atezolizumab-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Cross sectional imaging will be performed with either contrast enhanced CT or MRI. RECIST 1.1 (modified RECIST for pleural mesothelioma) criteria will be used to determine disease response.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Response will be assessed by an independent, blinded radiologist at the MD Anderson Quantitative Imaging Analysis Core using RECIST v1.1 (see Appendix 3) and immune-modified RECIST (see Appendix 4). Pleural Mesothelioma will use modified RECIST as in the Appendix 5. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Genentech Inc for analysis:

- Blood samples for exploratory research on biomarkers
- Fresh tumor tissue sample collected at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

  Tissue should be collected by excisional or core needle biopsy, typically using a 21-18 gauge needle. The biopsy should include at least 5 cores, 2 FFPE and 3 fresh frozen. It should be collected within 28 days prior to initiation of protocol therapy.
- Tumor tissue sample collected at week 3 and at time of progression for exploratory research on biomarkers

  Biopsies at week 3 should be performed within 7 days before or after the administration of C2D1 of study therapy (with prior to therapy preferred). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, immunohistochemistry for PD-L1, multiplexed immunofluorescence for immune markers, flow cytometry, analysis of ctDNA concentration, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of germline or somatic mutations, and use of WGS or NGS.

For the neuroendocrine tumor cohorts, exploratory biomarkers will also include antibody titers to GAD and IA-2, assessed at baseline and after 3 weeks of treatment.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final manuscript has been completed, with the following exceptions:

- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Blood, plasma, serum, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final manuscript has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to patients unless required by law.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible.

Patients receiving bevacizumab should be carefully monitored for clinical signs and symptoms of congestive heart failure, especially in patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF should also be considered (echocardiogram or MUGA).

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Mandatory Samples for Whole Genome Sequencing

Blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) to identify germline or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research and the WGS portion of the Informed Consent Form by the Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in

aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from WGS specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Genentech, Inc. policy on study data publication.

4.5.8.1 Guidelines for Return of Incidental Results:

The decision-making for return of incidental results will be made as approved by the MD Anderson Cancer Center IRB in protocol PA12-1099 and described herein: Return of incidental results guidelines are being generated for common genetic alterations by a Return of Results Committee via Consultation between Institute of Personalized Cancer Therapy, Clinical Cancer Genetics, Molecular Diagnostic Laboratory, and Behavioral Science. Rarer alterations will be discussed on a case by case basis by the Return of Results Committee with input from Clinical Cancer Genetics, and selected cases will be discussed in person or virtually in the Molecular Tumor Board. The treating investigator will initiate return of results with genetic counseling based on recommendations of the Return of Results Committee. We will be initially reporting cancer-related genes only and only those that are clearly deleterious and actionable; we will expand our reporting to non-cancer related risk genes as we establish expertise in genetic counseling in this arena. This reporting will be congruent with the IRB-approved guidance for reporting of such results.

Patients with deleterious germline alterations who are alive but not under MD Anderson care will be contacted by treating investigator after discussion of the alteration in return of results committee and validation of the alteration in an anonymized fashion.

Genetic alterations will be considered to have “clinical utility” if the genetic risk associated with the variant is well-recognized and significant. Variants for which there would be clinical implications such as change in screening, chemoprevention or other behavior change, change in therapy or drug dose will be considered to have clinical utility. Variants that confer a high disease risk and that can be reduced by prevention/therapy would be especially prioritized for return.

We will initially consider return of results on cancer-related genes felt to have clinical utility. Please refer to protocol PA12-1099 for genes that are currently tested by our clinical cancer genetics program, as well as other cancer-related genes that may have clinical utility. These genes will be prioritized for discussion in the Return of Results Committee, and alterations in these genes will be specifically considered for return to patients with appropriate genetic counseling and CLIA validation. Notably, the actionability or clinical utility of any particular variant within a gene will also depend upon the pathogenicity of that variant as determined by the lab’s interpretation (e.g. polymorphism, low-penetrance susceptibility, variant of unknown significance, deleterious mutation associated with hereditary cancer). Examples of this include germline MET T1010I vs. MET mutations causative of hereditary papillary renal cancer, and APC I1307K vs. APC mutations causing FAP.

If an alteration is determined to have clinical utility based on guidelines developed, or based on assessment by the Return of Results Committee and/or by Clinical Cancer Genetics or by discussion at Molecular Tumor Board, next the alteration would be validated in a CLIA validated laboratory, in anonymized fashion, when possible. For cancer-related genes, this testing will be done using a unique “study identifier” rather than “patient identifiers” to protect the patient’s privacy. The testing may be outsourced to Medical Genetics Laboratories at Baylor, Myriad Genetics Illumina, Invitrae, Ambry, Guardant, Genomic Health, Broad Institute, Life Technologies/ThermoFisher, Complete Genomics etc. If MD Anderson develops CLIA tests for these alterations in the future, they may be done at MD Anderson. After confirmation of the alteration in a CLIA lab, patient will be contacted. The testing may identify conditions for which genetic counseling and germline testing in the CLIA environment is frequently facilitated in our institution (e.g. BRCA testing). If sample is not available for validation in a CLIA lab, results felt to be deleterious and high confidence as assessed by the Return of Incidental Results Committee may be returned to the patient without additional testing. Notably, to date all deleterious germline validations identified were successfully validated on a separate CLIA assay. For these alterations, the patient will be contacted by the treating investigator or genetic counselor, and invited for formal genetic counseling. Standard clinical counseling and CLIA testing will then be recommended for at-risk family members. Of note, in some unfortunate cases the patient may be deceased when the results of genomic testing become available, and the patient’s designated power of attorney will be contacted instead.

Return of incidental results to patients by the investigator or clinical cancer genetics team will be documented either with a telephone note or a clinic note.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab and bevacizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma), with the following exception:

  Atezolizumab-treated patients will be permitted to continue study treatment after experiencing radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) if they meet all of the following criteria:

  – Evidence of clinical benefit, as determined by the investigator following a review of all available data
  – Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
  – Absence of decline in ECOG Performance Status that can be attributed to disease progression
  – Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit $\leq$30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or Genentech, Inc. terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination
- Patient non-adherence to the study plan as determined by the investigator

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The PI has the right to terminate this study and one or more cohorts in the study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1 and 5.1.2). Guidelines for management of patients who experience specific adverse events are provided in Table 5 (see Section 5.1.3.3).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs, immune-related hepatitis, pneumonitis, nephritis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis. In addition, systemic immune activation (described below) is a potential risk associated with atezolizumab. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the PI for additional recommendations.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: hypertension, proteinuria, venous thromboembolism, arterial thromboembolism, gastrointestinal perforation, fistula, wound healing complications, hemorrhage, mucocutaneous hemorrhage, posterior reversible leukoencephalopathy, systolic heart failure, ovarian failure, neutropenia, and hypersensitivity and infusion reactions. Please refer to section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The bevacizumab dose will be based on the patient's weight at enrollment and will remain the same throughout the study, unless there is a weight change of > 10% from baseline. It is not necessary to correct dosing on the basis of ideal weight, unless warranted per institutional guidelines/standard. Management of bevacizumab may be performed according to the label.

5.1.3.2 Treatment Interruption

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 105 days, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 105 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Patients who discontinue atezolizumab either transiently or permanently (e.g., for adverse events) may continue on bevacizumab until disease progression if there is felt to be clinical benefit.

Patients who discontinue bevacizumab transiently or permanently for adverse events may continue on single-agent atezolizumab until disease progression if there is felt to be clinical benefit. Patients with Grade ≥ 3 toxicities attributable to bevacizumab should withhold atezolizumab until those toxicities have improved to Grade ≤ 2 (exception for Grade 3 hypertension). If bevacizumab is permanently discontinued but there is felt to be clinical benefit from atezolizumab, the latter may be continued.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. Patients who develop Grade 4 toxicities related to bevacizumab for > 21 days should permanently discontinue bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab should occur ≥ 28 days after surgery and after wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

Bevacizumab infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

5.1.3.3 Management Guidelines

Guidelines for management of patients who experience specific adverse events are provided in Table 5.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Atezolizumab:	
Anaphylaxis	• For anaphylaxis precautions, see Appendix 7.
IRRs	
Atezolizumab infusion-related reaction, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Interrupt or slow the rate of atezolizumab infusion • Continue bevacizumab.
Atezolizumab infusion-related reaction, Grade 3 or 4	• Permanently discontinue atezolizumab • Continue bevacizumab
Pulmonary events	
Pneumonitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pneumonitis, Grade 2	• Hold atezolizumab until resolution • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. If not, permanently discontinue bevacizumab. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.

Event	Action to Be Taken
Pneumonitis, Grade 3 or 4	• Permanently discontinue atezolizumab • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper. • Permanently discontinue bevacizumab.
Hepatotoxicity	
Immune-mediated hepatitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Immune-mediated hepatitis, Grade 2	• Hold atezolizumab until resolution • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper, for grade 2 elevation of transaminases, with or without bilirubin elevation. **Events of > 5 days' duration:** • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Immune-mediated hepatitis, Grade 3 or 4	• Permanently discontinue atezolizumab • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper • Permanently discontinue bevacizumab.
Hepatic event, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Hepatic event, Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. **Events of > 5 days' duration:** • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Hepatic event, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.

Event	Action to Be Taken
Diarrhea or colitis, Grade 2	• Hold atezolizumab • If symptoms persist for longer than 5 days or recur, administer 1-2mg/mg/day prednisone equivalent • When symptoms resolve to Grade 0 or 1, taper corticosteroids over at least 1 month • Resume treatment with atezolizumab if the event resolves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg/day oral prednisone or less. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diarrhea or colitis, Grade 3	• Hold atezolizumab • Administer 1-2mg/mg/day IV methylprednisolone • When symptoms resolve to Grade 0 or 1, taper corticosteroids over at least 1 month • Resume treatment with atezolizumab if the event resolves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg/day oral prednisone or less. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Endocrine disorders	
Hypophysitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab
Hypophysitis, Grade 2 or 3	• Withhold atezolizumab • Administer corticosteroids and hormone replacement as clinically indicated • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Hypophysitis, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.

Event	Action to Be Taken
Asymptomatic hypothyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Symptomatic hypothyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab and begin thyroid replacement therapy as needed • Isolated hypothyroidism should be managed with replacement therapy and without corticosteroids • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Withhold bevacizumab. • Resume bevacizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab and initiate an anti-thyroid drug as indicated. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Withhold bevacizumab. • Resume bevacizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue bevacizumab for life-threatening immune-related hyperthyroidism.

Event	Action to Be Taken
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once symptoms resolve. • Taper corticosteroids over at least 1 months when symptoms improve to Grade 0 or 1. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone, and the patient is stable on replacement therapy. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diabetes Mellitus, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Initiate treatment with insulin for type I diabetes mellitus • Continue bevacizumab.
Diabetes Mellitus, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Resume atezolizumab when metabolic control is achieved on insulin replacement therapy. • Withhold bevacizumab. • Resume bevacizumab when symptoms resolve and glucose levels are stable.
Ocular toxicity	
Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.

Event	Action to Be Taken
Pancreatic toxicity	
Amylase and/or lipase elevation, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Amylase or lipase elevation, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks, and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue bevacizumab.
Immune-related pancreatitis, Grade 2 or 3	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue bevacizumab.
Immune-related pancreatitis, Grade 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Recurrent pancreatitis of any grade is to be considered a grade 4 event. • Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Infection	

Event	Action to Be Taken
Infection, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Follow guidelines provided in the Bevacizumab Package Insert and Investigator's Brochure.
Infection, Grade 3	• Withhold atezolizumab • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. • Withhold bevacizumab • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Infection, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Dermatologic toxicity	
Rash, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Rash, Grade 3	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Rash, Grade 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.
Neurologic disorders	
Immune-related neuropathy, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.

Event	Action to Be Taken
Immune-related neuropathy, Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Institute medical intervention as appropriate • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks
Immune-related neuropathy, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Institute medical intervention as appropriate • Permanently discontinue bevacizumab.
Myasthenia gravis and Guillain-Barré, all grades	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Institute medical intervention as appropriate • Consider initiation of systemic corticosteroids at a dose of 1-2mg/kg/day oral prednisone. • Permanently discontinue bevacizumab.
Immune-related meningitis or encephalitis, all grades	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves. • Taper corticosteroids over at least 1 months when symptoms improve to Grade 0 or 1. • Permanently discontinue bevacizumab.
Nephritis	
Nephritis, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.

Event	Action to Be Taken
Nephritis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Nephritis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Bevacizumab: **Hypertension**	
Grade 1	No dose modification
Grade 2	• Withhold bevacizumab. Start antihypertensive therapy per institutional policy. Patient may resume bevacizumab after blood pressure < 150/90 mmHg.
Grade 3	• Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	• Discontinue bevacizumab
Hemorrhage	
Grade 1 or 2, non-CNS, non-pulmonary events	• No bevacizumab modification
Grade 3 non-CNS, non-pulmonary events	• Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. • Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab.

Event	Action to Be Taken
Grade 4 non-CNS, non-pulmonary events	• Discontinue bevacizumab
Grade 1 pulmonary events	• Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary events	• Discontinue bevacizumab
CNS hemorrhage, any grade	• Discontinue bevacizumab
Venous thromboembolism	
Grade 1 or 2	• No bevacizumab modification
Grade 3 or asymptomatic Grade 4	• If the planned duration of full-dose anticoagulation is < 2 weeks bevacizumab should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	• Discontinue bevacizumab
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	• Discontinue bevacizumab permanently.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
Grade 1 or 2	• No bevacizumab modification
Grade 3	• Withhold bevacizumab until resolution to Grade $\leqslant$ 1.
Grade 4	• Discontinue bevacizumab.
Proteinuria	
Grade 1 (urine dipstick 1^+ or urine collection 0.15 to 1.0 g/24 hr)	• No bevacizumab modification

Event	Action to Be Taken
Grade 2 (urine dipstick 2^+-3^+ or urine collection >1.0 to to 3.5 g/24 hr)	• For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose. • For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab. • Withhold bevacizumab for proteinuria > 2 g/24hr and resume when proteinuria is $\leqslant$ 2 g/24hr.
Grade 3 (urine dipstick 4^+ or urine collection > 3.5 g/24 hr)	• Withhold bevacizumab. • Resume bevacizumab when proteinuria $\leqslant$ 2g/24h[a]
Grade 4 (nephrotic syndrome)	• Discontinue bevacizumab.
GI Perforation	
Any grade	• Discontinue bevacizumab.
Fistula	
Any grade tracheoesophageal fistula	• Discontinue bevacizumab.
Grade 4 fistula (other than tracheoesophegeal)	• Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	• Continue bevacizumab for partial obstruction not requiring medical intevervention.
Grade $\geqslant$ 2	• Discontinue bevacizumab.
Wound Dehiscence	
Any grade	• Discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy	
Any grade	• Discontinue bevacizumab.

IRR = infusion-related reaction; TSH = thyroid-stimulating hormone.

[a] All proteinuria values are from 24-hour urine collections

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor and to Genentech Inc, as outlined in Section 5.4.

5.2.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Genentech Inc products, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Adverse events may occur during the course of the use of Genentech Inc products in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events (regardless of grade or attribution) that occur after the consent form is signed but before treatment initiation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment initiation through 90 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 5.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to Genentech Inc)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

Adverse Events of Special Interest (Immediately Reportable to the Sponsor and Genentech Inc)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Atezolizumab AEs of Special Interest

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Bevacizumab AEs of Special Interest

- Hypertension ≥ grade 3

- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (or RPLS; any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ⩾ grade 2

5.2.3 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Immune-mediated adverse events, including conditions (regardless of grade) suggestive of an autoimmune disorder, such as Grade ≥ 3 rash or pruritus, Grade ≥ 3 diarrhea or Grade ≥ 2 colitis.

Cases of potential drug-induced liver injury that include Grade ≥ 3 asymptomatic AST/ALT/total bilirubin elevations, or Grade ≥ 2 AST/ALT/total bilirubin elevations with constitutional symptoms (Hy's law, see Section 5.3.5.6)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor and Genentech Inc in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events (all grades and attributions), whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The PI or designee will be responsible for assigning attribution of adverse events to the study agent.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms

cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the underlying malignancy should be recorded on the eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor and Genentech Inc (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the

cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Deaths that occur after the adverse eventreporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Underlying Malignancy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1 criteria (modified RECIST for pleural mesothelioma). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR AND GENENTECH INC

Certain events require immediate reporting to allow the Sponsor and Genentech Inc to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor and Genentech Inc immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor and Genentech Inc within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (see Section 5.4.1 for further details)
- Adverse events of special interest (see Section 5.4.1 for further details)
- Pregnancies (see Section 5.4.2 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

For reporting of adverse events to Genentech, Inc., reports should be faxed to GNE fax number (650) 238-6067 or sent via email to usds_aereporting-d@gene.com.

5.4.1 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.1.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment (or until initiation of new systemic anti-cancer therapy, whichever occurs first). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$90 days after the last dose of study treatment are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.2.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

5.4.2.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.2.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Supporter Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, Genentech Inc or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The PI or designee will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the PI or designee will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Bevacizumab Investigator's Brochure

The PI or designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a phase II study to assess the efficacy of atezolizumab combined with bevacizumab in 8 rare solid tumor groups:

1. Appendiceal adenocarcinoma, KRAS-wild type
2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
3. Human Papilloma Virus-associated cancers
4. Merkel cell carcinoma
5. Neuroendocrine tumors, pancreatic
6. Neuroendocrine tumors, extrapancreatic
7. Peritoneal mesothelioma
8. Pleural mesothelioma

The primary endpoint is the overall best response since the start of the treatment. A total of 136 patients will be enrolled, i.e., 20 patients in each tumor group, except for Cohort 2, nasopharyngeal carcinoma, which will be terminated after 4 patients are enrolled, and Cohort 4, Merkel cell carcinoma, which will be terminated after 12 patients have been enrolled. Considering the rarity of the diseases, the patient accrual rate is approximately 1 to 2 patients per month per tumor group. And the total duration of the study will be up to 30 months.

6.1 DETERMINATION OF SAMPLE SIZE

For each tumor group, we will estimate the best response rate and its 95% confidence interval (CI). When the sample size is 20, and the response rate is 0.3, the two-sided 95% exact confidence interval using the Clopper and Pearson method will be (0.119, 0.543). The exact 95% CI is calculated for various scenarios of true best response rate in Table 9.

Table 8 The exact 95% CI is calculated for various scenarios of true best response rate

Sample Size (N)	Best response rate	95% exact CI
20	0.3	(0.119, 0.543)
20	0.2	(0.057, 0.437)
20	0.1	(0.012, 0.317)

The table below lists the response rate p_0 based on the historical data for each group.

Table 9 The best response rate based on historical data

	Tumor Type	p_0
1	Appendiceal adenocarcinoma, KRAS-wild type	1%
2	Epstein-Barr Virus-associated nasopharyngeal carcinoma	10%
3	Human Papilloma Virus-associated cancers	5%
4	Merkel cell carcinoma	5%
5	Neuroendocrine tumors, pancreatic	10%
6	Neuroendocrine tumors, extrapancreatic	5%
7	Peritoneal mesothelioma	1%
8	Pleural mesothelioma	5%

6.2 SUMMARIES OF CONDUCT OF STUDY

This is a basket trial of eight parallel phase II trials of the combination of Atezolizumab and Bevacizumab in rare cancer patients. Enrollment, study drug administration, and discontinuation from the study will be summarized by all patients and tumor group. The reasons for study drug discontinuation will be also tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by tumor group.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographic information (e.g. age, gender) at baseline will be analyzed, with data summarized in mean ± standard deviation, median and range for continuous variables, and in frequency count and percentage for categorical variables. The student t-test or the Wilcoxon test may be used to compare continuous variables among different tumor patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all patients who received at least one dose of the study drug.

6.4.1 Primary Efficacy Endpoint

The primary outcome is the overall best response rate (PR or CR) since the start of treatment, with the primary analysis performed no less than six months after the final patient is enrolled. For each tumor group, we will estimate the best response rate and its 95% exact confidence interval using the Clopper and Pearson method. And we will assess the efficacy of the combination treatment by performing the independent binomial test comparing the best response rate versus the historical control for each tumor group. Considering the limited sample size for each tumor group, we may apply the Bayesian classification and information sharing method proposed by Lee and Chen (submitted) in the data analysis. It will provide a more efficient and more powerful way to estimate and test the response rate for similarly performed groups. We will first cluster the tumor groups according to their response rate into the low- or high-response cluster first, and then apply the Bayesian hierarchical model to borrow information among groups within the same cluster in estimating their response rate and comparing it to the historical control.

6.4.2 Secondary Efficacy Endpoints

For each tumor group, median DOR and corresponding 2-sided 95% CI will be reported.

Time-to-event outcomes, including progression free survival (PFS) and overall survival (OS), will be estimated using Kaplan-Meier method. Patients discontinuing treatment for reasons other than toxicity (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination, or death, whichever occurs first. Patients who discontinue study treatment for reasons other than withdrawal of consent will be followed for survival and subsequent ant-cancer therapies approximately every 3 months until death, loss to follow–up, withdrawal of consent, or study termination. During this period, documentation of anti-cancer therapies should include administration start and stop dates. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model may be utilized to include multiple covariates in the time-to-event analysis.

6.4.3 Exploratory Efficacy Endpoints

Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each tumor group. The time-course of biomarker measures will be investigated graphically. If there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic

regression will be used to explore possible associations between biomarker measures and clinical outcomes.

6.5 SAFETY ANALYSES

The safety analyses will include all patients who received at least one dose of study treatment, with patients grouped according to treatment received.

Verbatim adverse events and severity will be graded according to NCI CTCAE v4.0.

The safety analyses will include all patients who received at least one dose of study treatment. Toxicity data will be summarized by frequency tables for each tumor type group. The association between the types and severity of toxicity and the tumor group will be evaluated. No formal statistical testing will be performed on these summaries.

6.6 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with treatment response, including efficacy and/or adverse events. Biomarker analyses may be reported in a separate report.

6.7 INTERIM ANALYSES

6.7.1 Interim Safety Monitoring

For patient safety, A Bayesian toxicity monitoring rule will be implemented for the treatment related toxicity events during the duration of the treatment in all treated patients across 8 tumor groups.

A toxicity event is defined as:

---All non-hematologic AEs Grade $\geqslant$ 3 with the exceptions of:

- Grade 3 Hypertension
- Grade 3 Nausea
- Grade ≥ 3 Diarrhea if reversible within 48 hours with maximal supportive care
- Electrolyte abnormalities that are reversible within 72 hours with supportive care and/or supplementation

---All hematologic AEs Grade $\geqslant$ 4

---Pneumonitis
---Colitis
---Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism or hypophysitis
---Hepatitis, defined as AST or ALT $>10\times$ ULN
---Systemic lupus erythematosus
---Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
---Hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation

---Nephritis
---Ocular toxicities (e.g. uveitis, retinitis)
---Myositis
---Myopathies, including rhabdomyolysis
---Grade ≥2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
---GI perforation, abscesses and fistulae (any grade)
---CNS bleeding
---Haemoptysis ≥ grade 2
---Arterial thromboembolic events (any grade)
---PRES (or RPLS; any grade)
---Non-GI fistula or abscess ⩾ grade 2

Let p.tox be the toxicity probability, then if Pr [p. tox > 0.3] >0.9, we will terminate the study early. The protocol statistician will apply the monitoring every 5 patients for the first 20 patients, then every 10 for the rest of study. That is, we will early stop the study if we observe [# patients experiencing toxicity] / [#patients being treated] >= 4/5, 6/10, 8/15, 9/20, 13/30, 16/40, 20/50, 23/60, 27/70, 30/80, 33/90, 37/100, 40/110, 43/120, 46/130, 50/140, 53/150, or 56/160. The operating characteristic for applying this toxicity monitoring rule is shown in the table below.

Table 10 Operating characteristics for toxicity early stopping based 5000 simulation runs per scenario

True toxicity probability	Early stopping probability	Average sample size
0.2	0.021	157.0
0.3	0.317	123.8
0.4	0.950	47.1
0.5	0.999	19.1

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The University of Texas MD Anderson Cancer Center will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. The PI will perform oversight of the data management of this study.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at The University of Texas MD Anderson Cancer Center and records retention for the study data will be consistent with The University of Texas MD Anderson Cancer Center's standard procedures, which mandate that data be maintained indefinitely.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of the MD Anderson Cancer Center Prometheus EDC system.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

SAE data will be captured via eSAE in accordance with Sponsor policy.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site’s computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that

shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator indefinitely, in accordance with the current policy of the MD Anderson Cancer Center IND office.

Written notification should be provided to the Sponsor and Genentech Inc prior to transferring any records to another party or moving them to another location.

7.6 MONITORING

During the study, a study monitor from the University of Texas MD Anderson Cancer Center Investigational New Drug Office will have regular contacts with the investigator and team.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a

patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor and Genentech Inc with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol

amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

The Investigator is responsible for completing the cohort summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 5 evaluable patients, and every 5 evaluable patients, thereafter.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and Genentech Inc and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 ADMINISTRATIVE STRUCTURE

This trial will be supported via the rare disease strategic alliance between The University of Texas MD Anderson Cancer Center and Genentech. The University of Texas MD Anderson Cancer Center will be the sole site, responsible for enrolling approximately 160 total patients.

The MD Anderson Cancer Center IND office will provide oversight of safety (see Section 5.2).

After written informed consent has been obtained, the study team will generate a unique study identification number for the patient.

Patient data will be recorded via an EDC system with use of eCRFs.

Central laboratories, including those at Genentech/Roche/Roche collaborators and at The University of Texas MD Anderson Cancer Center, will be used for PD-L1 expression status determination and will provide kits for pharmacogenomic, tissue, whole blood, serum, and plasma sample analyses to be conducted at central laboratories or Genentech.

Treatment decisions will be made on the basis of the local reading of ECGs obtained during the study.

Imaging data will be retained at The University of Texas MD Anderson Cancer Center.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor and Genentech Inc is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all

requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to Genentech Inc prior to submission for publication or presentation. This allows Genentech Inc to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Genentech Inc will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Genentech Inc personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Genentech Inc personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Genentech Inc, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in contact information).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol 2012;30:507–12.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634–46.

DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277–80.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. 2012 Dec. EMA/CHPM/205/95/Rev.4.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Fozza C, Corda G, Virdis P, et al. Derangement of the T-cell repertoire in patients with B-cell non–Hodgkin's lymphoma. Eur J Haematol 2014:1–12.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. J Clin Oncol 2006;24:5545–51.

[FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007 May.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression-free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. BMJ Open 2013;3:1–6.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;12:528–38.

Postow M, Manuel M, Wong P, et al. T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma. J Immunother Cancer 2014;2(Suppl 3):08.

Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a atezolizumab study. J Clin Oncol 2013;31:abstract 3001.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12):2367–75.

Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006;355:2542–50.

Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 2010;11:861–70.

Stinchcombe TE, Socinski MA, Lee CB, et al. Considerations for second-line therapy of non-small cell lung cancer. Oncologist 2008;13:128–36.

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. New Engl J Med 2010;363:733–42.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Appendix 1

Schedule of Activities

	Screening [a]	Odd Treatment Cycles (21-day cycles)	Cycle 1 only	Even Treatment Cycles (21-day cycles)	Cycle 2 only	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±7 days)	Day 8 (±3 days)	Day 1 (±7 days)	Day 8 (±3 days)	≤30 Days after Last Dose	
Informed consent	x [c]						
Demographic data	x						
Medical history and baseline conditions	x						
Vital signs [e]	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	
Height	x						
Complete physical examination [f]	x					x	
Limited physical examination [g]		x	x	x	x		
ECOG Performance Status	x	x	x	x	x	x	
ECG [h]	x						
Hematology [i]	x [j]	x [k]	x	x	x	x	
Chemistry [l]	x [j]	x [k]	x	x	x	x	

Appendix 1
Schedule of Activities (cont.)

	Screening [a]	Odd Treatment Cycles (21-day cycles)	Cycle 1 only	Even Treatment Cycles (21-day cycles)	Cycle 2 only	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±7 days)	Day 8 (±3 days)	Day 1 (±7 days)	Day 8 (±3 days)	≤30 Days after Last Dose	
Pregnancy test [m]	x [j]						
Coagulation (INR, aPTT)	x [j]					x	
TSH, free T3 (or total T3 [n]), free T4	x [j]	x [n]				x	
Viral serology [o]	x [j]						
Urinalysis [p]	x [j]	x [q]					
Echo/MUGA	x [r]	x [r]		x [r]			
Blood sample for biomarkers	x [s]			x [s]		x [s]	x [s]
Blood sample for WGS	x						
Tumor biopsy (if clinically feasible)	x			X [t]		X [u]	
Tumor response assessments	x [v]	x [w,x]		x [w,x]			
Concomitant medications [y]	x [y]	x	x	x	x	x	
Adverse events [z]	x [z]	x [z]	x [z]	x [z]	x [z]	x	x [z]
Study treatment administration [aa]		x		x			
Survival follow-up and anti-cancer treatment							x [bb]

Appendix 1
Schedule of Activities (cont.)

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 30 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] A pretreatment tumor biopsy is required.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline on the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.

[m] All women of childbearing potential will have a serum pregnancy test at screening.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter.

Appendix 1
Schedule of Activities (cont.)

[o] At screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[q] Urinalysis should be performed every 6 weeks (2 cycles) during study treatment.

[r] Echo or MUGA to be considered at baseline and thereafter per clinical suspicion

[s] See Appendix 2 for detailed schedule.

[t] On-treatment biopsy will be obtained on Cycle 2 Day 1, +/- 7 days (prior to C2D1 preferred)

[u] Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.

[v] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 (modified RECIST for pleural mesothelioma) may be used.

[w] Patients will undergo tumor assessments at baseline and every 9-12 weeks thereafter (with neuroendocrine cohorts 5 and 6 assessed every 12 weeks and all other cohorts assessed every 9 weeks), regardless of dose delays, until radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) or (for atezolizumab-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Appendix 1
Schedule of Activities (cont.)

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor and Genentech Inc should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[aa] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day −28 to Day –1)	NA	Biomarker (blood, plasma, and serum) In cohorts 5 and 6 (neuroendocrine tumors), antibody titers to GAD and IA-2 will be assessed in the CLIA environment.
Day 1 of Cycle 2	Prior to infusion	Biomarker (blood, plasma, and serum) In cohorts 5 and 6 (neuroendocrine tumors), antibody titers to GAD and IA-2 will be assessed in the CLIA environment.
Progression (≤ 40 days after progression is radiographically determined)	NA	Biomarker (blood, plasma, and serum)

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥ 10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be

taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm)

should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to <10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥ 30% decrease in tumor burden, [a] in the absence of CR
PD	≥ 20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥ 20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 mm but $<$15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

<u>ASSESSMENT OF TUMOR BURDEN</u>

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and

measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non–lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is $<$10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is $\geq$15 mm.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to $<$15 mm (or even $<$10 mm). However, if it subsequently decreases to $<$10 mm and all other lesions are no longer detectable or have also decreased to a short axis of $<$10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to $<$10 mm during the study. Thus, when lymph nodes are included in the sum of diameters,

the sum may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the

complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

Definitions of the criteria used to determine objective tumor response are provided below:

- Complete response (CR): Disappearance of all lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

  New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target or measurable new lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 1.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Can 2014;2:17

Appendix 5 Modified RECIST criteria for Malignant Pleural Mesothelioma

As previously described (Byrne and Nowak, 2004), RECIST 1.1 (Appendix 3) does not adequately describe the volume of pleural mesothelioma, and a modified RECIST system is a superior predictor of patient disease burden and outcome.

With the exception of measurement of pleural lesions, modified RECIST is identical to RECIST 1.1, as described in Appendix 3. Rather than reiterate the common elements of RECIST 1.1 and modified RECIST, we will focus here on the specific details of measuring pleural thickness using modified RECIST as described (Byrne and Nowak, 2004).

Tumor thickness perpendicular to the chest wall or mediastinum is measured in two positions at three separate levels on transverse cuts at least 1 cm apart and related to anatomical landmarks of CT scan. The sum of the six measurements defines a unidimensional pleural measure. Transverse cuts above the level of division of the main bronchi are preferred if at all possible.

At reassessment, pleural thickness is measured at the same position at the same level, ideally by the same observer.

Other measurable lesions are measured unidimensionally as per the RECIST criteria in Appendix 3. Unidimensional measurements are summed to obtain the total tumor measurement. Response criteria are identical to RECIST 1.1 (Appendix 3).

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations

Appendix 8
Additional References

ALAKUS, H., BABICKY, M. L., GHOSH, P., YOST, S., JEPSEN, K., DAI, Y., ARIAS, A., SAMUELS, M. L., MOSE, E. S., SCHWAB, R. B., PETERSON, M. R., LOWY, A. M., FRAZER, K. A. & HARISMENDY, O. 2014. Genome-wide mutational landscape of mucinous carcinomatosis peritonei of appendiceal origin. *Genome Med,* 6**,** 43.

ASARE, E. A., COMPTON, C. C., HANNA, N. N., KOSINSKI, L. A., WASHINGTON, M. K., KAKAR, S., WEISER, M. R. & OVERMAN, M. J. 2016. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: Analysis of the National Cancer Data Base. *Cancer,* 122**,** 213-21.

BARBER, D. L., WHERRY, E. J., MASOPUST, D., ZHU, B., ALLISON, J. P., SHARPE, A. H., FREEMAN, G. J. & AHMED, R. 2006. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature,* 439**,** 682-7.

BENNOUNA, J., SASTRE, J., ARNOLD, D., OSTERLUND, P., GREIL, R., VAN CUTSEM, E., VON MOOS, R., VIEITEZ, J. M., BOUCHE, O., BORG, C., STEFFENS, C. C., ALONSO-ORDUNA, V., SCHLICHTING, C., REYES-RIVERA, I., BENDAHMANE, B., ANDRE, T., KUBICKA, S. & INVESTIGATORS, M. L. S. 2013. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol,* 14**,** 29-37.

BHATIA, S., AFANASIEV, O. & NGHIEM, P. 2011. Immunobiology of Merkel cell carcinoma: implications for immunotherapy of a polyomavirus-associated cancer. *Curr Oncol Rep,* 13**,** 488-97.

BLANK, C., GAJEWSKI, T. F. & MACKENSEN, A. 2005. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol Immunother,* 54**,** 307-14.

BRAHMER, J., RIZVI, N., LUTZKY, J., KHLEIF, S., BLAKE-HASKINS, A., LI, X., ROBBINS, P., VASSELLI, J., IBRAHIM, R. & ANTONIA, S. 2014. Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. *Journal of Clinical Oncology* 32**,** Abstract 8021

BRAHMER, J. R. 2013. Harnessing the immune system for the treatment of non-small-cell lung cancer. *J Clin Oncol,* 31**,** 1021-8.

BRAHMER, J. R., TYKODI, S. S., CHOW, L. Q., HWU, W. J., TOPALIAN, S. L., HWU, P., DRAKE, C. G., CAMACHO, L. H., KAUH, J., ODUNSI, K., PITOT, H. C., HAMID, O., BHATIA, S., MARTINS, R., EATON, K., CHEN, S., SALAY, T. M., ALAPARTHY, S., GROSSO, J. F., KORMAN, A. J., PARKER, S. M., AGRAWAL, S., GOLDBERG, S. M., PARDOLL, D. M., GUPTA, A. & WIGGINTON, J. M. 2012. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med,* 366**,** 2455-65.

BRUNNER, M., THURNHER, D., PAMMER, J., GELEFF, S., HEIDUSCHKA, G., REINISCH, C. M., PETZELBAUER, P. & EROVIC, B. M. 2008. Expression of VEGF-A/C, VEGF-R2, PDGF-alpha/beta, c-kit, EGFR, Her-2/Neu, Mcl-1 and Bmi-1 in Merkel cell carcinoma. *Mod Pathol,* 21**,** 876-84.

Appendix 8
Additional References (cont.)

BYRNE, M. J. & NOWAK, A. K. 2004. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol,* 15**,** 257-60.

CALABRO, L., MORRA, A., FONSATTI, E., CUTAIA, O., AMATO, G., GIANNARELLI, D., DI GIACOMO, A. M., DANIELLI, R., ALTOMONTE, M., MUTTI, L. & MAIO, M. 2013. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *Lancet Oncol,* 14**,** 1104-11.

CAPLIN, M. E., PAVEL, M., CWIKLA, J. B., PHAN, A. T., RADERER, M., SEDLACKOVA, E., CADIOT, G., WOLIN, E. M., CAPDEVILA, J., WALL, L., RINDI, G., LANGLEY, A., MARTINEZ, S., BLUMBERG, J., RUSZNIEWSKI, P. & INVESTIGATORS, C. 2014. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med,* 371**,** 224-33.

CARR, N. J., CECIL, T. D., MOHAMED, F., SOBIN, L. H., SUGARBAKER, P. H., GONZALEZ-MORENO, S., TAFLAMPAS, P., CHAPMAN, S. & MORAN, B. J. 2016. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol,* 40**,** 14-26.

CHEN, D. S., IRVING, B. A. & HODI, F. S. 2012. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res,* 18**,** 6580-7.

CHUA, D. T., SHAM, J. S. & AU, G. K. 2003. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol,* 39**,** 361-6.

DAVIES, M. 2014. New modalities of cancer treatment for NSCLC: focus on immunotherapy. *Cancer Manag Res,* 6**,** 63-75.

DAY, C. L., KAUFMANN, D. E., KIEPIELA, P., BROWN, J. A., MOODLEY, E. S., REDDY, S., MACKEY, E. W., MILLER, J. D., LESLIE, A. J., DEPIERRES, C., MNCUBE, Z., DURAISWAMY, J., ZHU, B., EICHBAUM, Q., ALTFELD, M., WHERRY, E. J., COOVADIA, H. M., GOULDER, P. J., KLENERMAN, P., AHMED, R., FREEMAN, G. J. & WALKER, B. D. 2006. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature,* 443**,** 350-4.

FANG, W., ZHANG, J., HONG, S., ZHAN, J., CHEN, N., QIN, T., TANG, Y., ZHANG, Y., KANG, S., ZHOU, T., WU, X., LIANG, W., HU, Z., MA, Y., ZHAO, Y., TIAN, Y., YANG, Y., XUE, C., YAN, Y., HOU, X., HUANG, P., HUANG, Y., ZHAO, H. & ZHANG, L. 2014. EBV-driven LMP1 and IFN-gamma up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. *Oncotarget,* 5**,** 12189-202.

FEHRENBACHER, L., SPIRA, A., BALLINGER, M., KOWANETZ, M., VANSTEENKISTE, J., MAZIERES, J., PARK, K., SMITH, D., ARTAL-CORTES, A., LEWANSKI, C., BRAITEH, F., WATERKAMP, D., HE, P., ZOU, W., CHEN, D. S., YI, J., SANDLER, A., RITTMEYER, A. & GROUP, P. S. 2016. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet,* 387**,** 1837-46.

FENG, H., SHUDA, M., CHANG, Y. & MOORE, P. S. 2008. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science,* 319**,** 1096-100.

Appendix 8
Additional References (cont.)

FOO, K. F., TAN, E. H., LEONG, S. S., WEE, J. T., TAN, T., FONG, K. W., KOH, L., TAI, B. C., LIAN, L. G. & MACHIN, D. 2002. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol,* 13**,** 150-6.

FORMAN, D., DE MARTEL, C., LACEY, C. J., SOERJOMATARAM, I., LORTET-TIEULENT, J., BRUNI, L., VIGNAT, J., FERLAY, J., BRAY, F., PLUMMER, M. & FRANCESCHI, S. 2012. Global burden of human papillomavirus and related diseases. *Vaccine,* 30 Suppl 5**,** F12-23.

HODI, F. S., LAWRENCE, D., LEZCANO, C., WU, X., ZHOU, J., SASADA, T., ZENG, W., GIOBBIE-HURDER, A., ATKINS, M. B., IBRAHIM, N., FRIEDLANDER, P., FLAHERTY, K. T., MURPHY, G. F., RODIG, S., VELAZQUEZ, E. F., MIHM, M. C., JR., RUSSELL, S., DIPIRO, P. J., YAP, J. T., RAMAIYA, N., VAN DEN ABBEELE, A. D., GARGANO, M. & MCDERMOTT, D. 2014. Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res,* 2**,** 632-42.

HODI, F. S., O'DAY, S. J., MCDERMOTT, D. F., WEBER, R. W., SOSMAN, J. A., HAANEN, J. B., GONZALEZ, R., ROBERT, C., SCHADENDORF, D., HASSEL, J. C., AKERLEY, W., VAN DEN EERTWEGH, A. J., LUTZKY, J., LORIGAN, P., VAUBEL, J. M., LINETTE, G. P., HOGG, D., OTTENSMEIER, C. H., LEBBE, C., PESCHEL, C., QUIRT, I., CLARK, J. I., WOLCHOK, J. D., WEBER, J. S., TIAN, J., YELLIN, M. J., NICHOL, G. M., HOOS, A. & URBA, W. J. 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med,* 363**,** 711-23.

JANNE, P. A., WOZNIAK, A. J., BELANI, C. P., KEOHAN, M. L., ROSS, H. J., POLIKOFF, J. A., MINTZER, D. M., TAYLOR, L., ASHLAND, J., YE, Z., MONBERG, M. J. & OBASAJU, C. K. 2005. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer,* 7**,** 40-6.

KANTOFF, P. W., HIGANO, C. S., SHORE, N. D., BERGER, E. R., SMALL, E. J., PENSON, D. F., REDFERN, C. H., FERRARI, A. C., DREICER, R., SIMS, R. B., XU, Y., FROHLICH, M. W., SCHELLHAMMER, P. F. & INVESTIGATORS, I. S. 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med,* 363**,** 411-22.

KARIM, S. & LEIGHL, N. 2016. Pembrolizumab for the treatment of thoracic malignancies: current landscape and future directions. *Future Oncol,* 12**,** 9-23.

KEIR, M. E., BUTTE, M. J., FREEMAN, G. J. & SHARPE, A. H. 2008. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol,* 26**,** 677-704.

KOUVARAKI, M. A., AJANI, J. A., HOFF, P., WOLFF, R., EVANS, D. B., LOZANO, R. & YAO, J. C. 2004. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 22**,** 4762-71.

KRISHNA, S. M., JAMES, S. & BALARAM, P. 2006. Expression of VEGF as prognosticator in primary nasopharyngeal cancer and its relation to EBV status. *Virus Res,* 115**,** 85-90.

KUKKO, H., KOLJONEN, V., LASSUS, P., TUKIAINEN, E., HAGLUND, C. & BOHLING, T. 2007. Expression of vascular endothelial growth factor receptor-2 in Merkel cell carcinoma. *Anticancer Res,* 27**,** 2587-9.

Appendix 8
Additional References (cont.)

LEE, N. Y., ZHANG, Q., PFISTER, D. G., KIM, J., GARDEN, A. S., MECHALAKOS, J., HU, K., LE, Q. T., COLEVAS, A. D., GLISSON, B. S., CHAN, A. T. & ANG, K. K. 2012. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. *Lancet Oncol,* 13**,** 172-80.

LEMOS, B. D., STORER, B. E., IYER, J. G., PHILLIPS, J. L., BICHAKJIAN, C. K., FANG, L. C., JOHNSON, T. M., LIEGEOIS-KWON, N. J., OTLEY, C. C., PAULSON, K. G., ROSS, M. I., YU, S. S., ZEITOUNI, N. C., BYRD, D. R., SONDAK, V. K., GERSHENWALD, J. E., SOBER, A. J. & NGHIEM, P. 2010. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol,* 63**,** 751-61.

LIPSON, E. J., VINCENT, J. G., LOYO, M., KAGOHARA, L. T., LUBER, B. S., WANG, H., XU, H., NAYAR, S. K., WANG, T. S., SIDRANSKY, D., ANDERS, R. A., TOPALIAN, S. L. & TAUBE, J. M. 2013. PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. *Cancer Immunol Res,* 1**,** 54-63.

MANSFIELD, A., PEIKERT, T., RODEN, A., KRCO, C., HARRINGTON, S., DONG, H. & KWON, E. 2014. Programmed cell death 1 ligand 1 expression and association with survival in mesothelioma. *Journal of Thoracic Oncology,* 9 S7-S52.

MANZONI, M., ROVATI, B., RONZONI, M., LOUPAKIS, F., MARIUCCI, S., RICCI, V., GATTONI, E., SALVATORE, L., TINELLI, C., VILLA, E. & DANOVA, M. 2010. Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer. *Oncology,* 79**,** 187-96.

MCCUSKER, M. E., COTE, T. R., CLEGG, L. X. & SOBIN, L. H. 2002. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer,* 94**,** 3307-12.

MOERTEL, C. G., HANLEY, J. A. & JOHNSON, L. A. 1980. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *The New England journal of medicine,* 303**,** 1189-94.

MOERTEL, C. G., LEFKOPOULO, M., LIPSITZ, S., HAHN, R. G. & KLAASSEN, D. 1992. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *The New England journal of medicine,* 326**,** 519-23.

NGEOW, J., LIM, W. T., LEONG, S. S., ANG, M. K., TOH, C. K., GAO, F., CHOWBAY, B. & TAN, E. H. 2011. Docetaxel is effective in heavily pretreated patients with disseminated nasopharyngeal carcinoma. *Ann Oncol,* 22**,** 718-22.

NGHIEM, P. T., BHATIA, S., LIPSON, E. J., KUDCHADKAR, R. R., MILLER, N. J., ANNAMALAI, L., BERRY, S., CHARTASH, E. K., DAUD, A., FLING, S. P., FRIEDLANDER, P. A., KLUGER, H. M., KOHRT, H. E., LUNDGREN, L., MARGOLIN, K., MITCHELL, A., OLENCKI, T., PARDOLL, D. M., REDDY, S. A., SHANTHA, E. M., SHARFMAN, W. H., SHARON, E., SHEMANSKI, L. R., SHINOHARA, M. M., SUNSHINE, J. C., TAUBE, J. M., THOMPSON, J. A., TOWNSON, S. M., YEARLEY, J. H., TOPALIAN, S. L. & CHEEVER, M. A. 2016. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med,* 374**,** 2542-52.

Appendix 8
Additional References (cont.)

OXNARD, G. R., WILCOX, K. H., GONEN, M., POLOTSKY, M., HIRSCH, B. R. & SCHWARTZ, L. H. 2016. Response Rate as a Regulatory End Point in Single-Arm Studies of Advanced Solid Tumors. *JAMA Oncol,* 2**,** 772-9.

QIAN, C. N., ZHANG, C. Q., GUO, X., HONG, M. H., CAO, S. M., MAI, W. Y., MIN, H. Q. & ZENG, Y. X. 2000. Elevation of serum vascular endothelial growth factor in male patients with metastatic nasopharyngeal carcinoma. *Cancer,* 88**,** 255-61.

RAGHAV, K. P., SHETTY, A. V., KAZMI, S. M., ZHANG, N., MORRIS, J., TAGGART, M., FOURNIER, K., ROYAL, R., MANSFIELD, P., ENG, C., WOLFF, R. A. & OVERMAN, M. J. 2013. Impact of molecular alterations and targeted therapy in appendiceal adenocarcinomas. *Oncologist,* 18**,** 1270-7.

RAYMOND, E., DAHAN, L., RAOUL, J.-L., BANG, Y.-J., BORBATH, I., LOMBARD-BOHAS, C., VALLE, J., METRAKOS, P., SMITH, D., VINIK, A., CHEN, J.-S., HÖRSCH, D., HAMMEL, P., WIEDENMANN, B., VAN CUTSEM, E., PATYNA, S., LU, D. R., BLANCKMEISTER, C., CHAO, R. & RUSZNIEWSKI, P. 2011. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *The New England journal of medicine,* 364**,** 501-13.

RINKE, A., MULLER, H. H., SCHADE-BRITTINGER, C., KLOSE, K. J., BARTH, P., WIED, M., MAYER, C., AMINOSSADATI, B., PAPE, U. F., BLAKER, M., HARDER, J., ARNOLD, C., GRESS, T., ARNOLD, R. & GROUP, P. S. 2009. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol,* 27**,** 4656-63.

RODRIGUEZ, D., CHEUNG, M. C., HOUSRI, N. & KONIARIS, L. G. 2009. Malignant abdominal mesothelioma: defining the role of surgery. *J Surg Oncol,* 99**,** 51-7.

ROLLISON, D. E., GIULIANO, A. R. & BECKER, J. C. 2010. New virus associated with merkel cell carcinoma development. *J Natl Compr Canc Netw,* 8**,** 874-80.

ROSENBERG, J. E., HOFFMAN-CENSITS, J., POWLES, T., VAN DER HEIJDEN, M. S., BALAR, A. V., NECCHI, A., DAWSON, N., O'DONNELL, P. H., BALMANOUKIAN, A., LORIOT, Y., SRINIVAS, S., RETZ, M. M., GRIVAS, P., JOSEPH, R. W., GALSKY, M. D., FLEMING, M. T., PETRYLAK, D. P., PEREZ-GRACIA, J. L., BURRIS, H. A., CASTELLANO, D., CANIL, C., BELLMUNT, J., BAJORIN, D., NICKLES, D., BOURGON, R., FRAMPTON, G. M., CUI, N., MARIATHASAN, S., ABIDOYE, O., FINE, G. D. & DREICER, R. 2016. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet,* 387**,** 1909-20.

SMEENK, R. M., VERWAAL, V. J., ANTONINI, N. & ZOETMULDER, F. A. 2007. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg,* 245**,** 104-9.

STEBBING, J., POWLES, T., MCPHERSON, K., SHAMASH, J., WELLS, P., SHEAFF, M. T., SLATER, S., RUDD, R. M., FENNELL, D. & STEELE, J. P. 2009. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer,* 63**,** 94-7.

THOMAS, A. & HASSAN, R. 2012. Immunotherapies for non-small-cell lung cancer and mesothelioma. *Lancet Oncol,* 13**,** e301-10.

TSAO, A. S., WISTUBA, I., ROTH, J. A. & KINDLER, H. L. 2009. Malignant pleural mesothelioma. *J Clin Oncol,* 27**,** 2081-90.

Appendix 8
Additional References (cont.)

VAN MEERBEECK, J. P., BAAS, P., DEBRUYNE, C., GROEN, H. J., MANEGOLD, C., ARDIZZONI, A., GRIDELLI, C., VAN MARCK, E. A., LENTZ, M. & GIACCONE, G. 1999. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer,* 85**,** 2577-82.

VOGELZANG, N. J., RUSTHOVEN, J. J., SYMANOWSKI, J., DENHAM, C., KAUKEL, E., RUFFIE, P., GATZEMEIER, U., BOYER, M., EMRI, S., MANEGOLD, C., NIYIKIZA, C. & PAOLETTI, P. 2003. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol,* 21**,** 2636-44.

YAO, J. C., HASSAN, M., PHAN, A., DAGOHOY, C., LEARY, C., MARES, J. E., ABDALLA, E. K., FLEMING, J. B., VAUTHEY, J.-N., RASHID, A. & EVANS, D. B. 2008. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 26**,** 3063-72.

YAO, J. C., LOMBARD-BOHAS, C., BAUDIN, E., KVOLS, L. K., ROUGIER, P., RUSZNIEWSKI, P., HOOSEN, S., ST PETER, J., HAAS, T., LEBWOHL, D., VAN CUTSEM, E., KULKE, M. H., HOBDAY, T. J., O'DORISIO, T. M., SHAH, M. H., CADIOT, G., LUPPI, G., POSEY, J. A. & WIEDENMANN, B. 2010. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 28**,** 69-76.

ZALCMAN, G., MAZIERES, J., MARGERY, J., GREILLIER, L., AUDIGIER-VALETTE, C., MORO-SIBILOT, D., MOLINIER, O., CORRE, R., MONNET, I., GOUNANT, V., RIVIERE, F., JANICOT, H., GERVAIS, R., LOCHER, C., MILLERON, B., TRAN, Q., LEBITASY, M. P., MORIN, F., CREVEUIL, C., PARIENTI, J. J., SCHERPEREEL, A. & FRENCH COOPERATIVE THORACIC, I. 2015. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*.

ZALCMAN, G., MAZIERES, J., MARGERY, J., GREILLIER, L., AUDIGIER-VALETTE, C., MORO-SIBILOT, D., MOLINIER, O., CORRE, R., MONNET, I., GOUNANT, V., RIVIERE, F., JANICOT, H., GERVAIS, R., LOCHER, C., MILLERON, B., TRAN, Q., LEBITASY, M. P., MORIN, F., CREVEUIL, C., PARIENTI, J. J., SCHERPEREEL, A. & FRENCH COOPERATIVE THORACIC, I. 2016. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet,* 387**,** 1405-14.

Original protocol

PROTOCOL

TITLE:	**A PHASE II, SINGLE-ARM OPEN-LABEL STUDY OF THE COMBINATION OF ATEZOLIZUMAB AND BEVACIZUMAB IN RARE SOLID TUMORS**
MD ANDERSON CANCER CENTER PROTOCOL NUMBER	2016-0861
GENENTECH PROTOCOL NUMBER:	ML39572
VERSION NUMBER:	3
VERSION DATE	3/6/2017
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	133805
INVESTIGATOR	Daniel M. Halperin, MD 1515 Holcombe Blvd Unit 426 Houston, TX 77030 Telephone: 713-792-2828 Fax: 713-745-1163 E-mail: dmhalperin@mdanderson.org
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab
MEDICAL MONITOR:	UT M.D. Anderson IND Office
SPONSOR:	UT M.D. Anderson
DATE FINAL:	See electronic date stamp below

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
LPLV	last patient, last visit
MTD	maximum tolerated dose
NCI	National Cancer Institute
NET	Neuroendocrine Tumor
ORR	objective response rate
PI	Principal investigator
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q3W	every 3 weeks
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
TC	tumor cell
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON THE SPECIFIC SOLID TUMORS BEING STUDIED

1.1.1 Appendiceal adenocarcinoma

Appendiceal tumors are rare, with an age-adjusted incidence of 0.12 cases per 1,000,000 per year.(McCusker et al., 2002) Metastatic appendiceal neoplasms are tumors characterized by a relatively indolent natural clinical course if low-grade and very aggressive biology if high grade.(Asare et al., 2016, Carr et al., 2016) Cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard therapy in low-grade tumors and results in prolonged survival, but is not effective in high grade tumors, where systemic therapy is the only option, but has limited benefit.(Smeenk et al., 2007) However, high tumor burden and medical comorbidities can exclude patients from curative intent surgery. Conventional cytotoxic chemotherapy in these patients has shown no or little clinical benefit.(Asare et al., 2016) There exists an unmet need for active targeted agents in this setting. Emerging data has shown a higher frequency of KRAS mutations in low-grade appendiceal neoplasms (70%-80%) compared to high-grade tumors.(Raghav et al., 2013, Alakus et al., 2014) Appendiceal adenocarcinomas mimic colorectal cancer to a large extent and are treated similarly. Immunotherapy has only been effective in microsatellite-unstable colorectal cancer, and novel strategies of immunomodulation are therefore needed in the treatment of cancers of the lower gastrointestinal tract.

1.1.2 Epstein-Barr Virus-associated nasopharyngeal carcinoma

Approximately 3,200 cases of nasopharyngeal carcinoma (NPC) are diagnosed yearly in the USA. Unfortunately, there are no standard of care systemic treatments for patients with recurrent or metastatic NPC. Platinum-based chemotherapy is frequently used in the first line setting. In the second line and beyond, monotherapy regimens with gemcitabine, capecitabine, or docetaxel(Chua et al., 2003, Foo et al., 2002, Ngeow et al., 2011) are frequently used, with responses rates of approximately 30% and a median PFS of only 5 months.

NPC is an Epstein Barr Virus (EBV) driven malignancy. Chronic EBV infection leads to increased viral EBV load and expression of PD-1 on cytotoxic memory T-cells leading to T-cell exhaustion (Barber et al., 2006, Day et al., 2006). Increased PD-1 expression also occurs in the virally affected host cells. Latent EBV infection is also associated with expression of LMP-1 protein which induces PD-L1 expression (Fang et al., 2014). Increased PD-1 and PD-L1 work together to suppress the immune system, leading to decreased EBV cellular immunity. PD-L1 expression is almost universal in NPC (98% of cases) and clinical activity of PD-1 inhibitor single agent has been reported in a cohort of patients with refractory NPC [Hsu, ESMO 2015].

VEGF concentrations are substantially increased in patients with metastatic NPC(Qian et al., 2000). The higher expression of VEGF in EBV related tumors is related to higher rates of recurrence and shorter overall survival(Krishna et al., 2006). Bevacizumab given

with concurrent chemoradiation has been studied in NPC with promising results (Lee et al., 2012). VEGF suppresses the immune system and the combination of bevacizumab with checkpoint inhibitor has rendered encouraging results in metastatic melanoma (Hodi et al., 2014). Taken together, there is a strong rationale to study the anti-PD-L1/anti-VEGF combination in metastatic NPC, a highly unmet clinical need.

1.1.3 Human Papilloma Virus (HPV)-associated cancers

The human papilloma virus (HPV) is associated with the development of multiple malignancies including cervical, oropharyngeal, vulvar, vagina, penile, and anal cancer. In 2008, of the estimated 12.7 million cancers, 610,000 cases are believed to be attributed to HPV (Forman et al., 2012). It is estimated 89,000 patients will be diagnosed worldwide with the rare HPV associated cancers: vulvar, vagina, penile, and anal cancer [Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 2016- 02-25. [7/15/16]. The association of HPV has been well documented in both cervical and oropharyngeal cancer, as well. Each of these cancers has been linked to HPV in variable degrees: 90% of anal, cervical, and vaginal carcinomas; 70% of all vulvar cancers; and 50% of penile cancers. Currently, there is no standard treatment approach for patients with metastatic disease for these rare cancers, nor is there a standard of care for cervical cancer refractory to platinum-based chemotherapy. In short, clinical trial development has been lacking for these malignancies. Yet, there is a rising incidence of HPV associated cancers, notably anal and oropharyngeal cancers (www.seer.gov). Identification of treatment options for the HPV associated malignancies of metastatic or surgically unresectable anal, penile, and vaginal, vulvar, and refractory cervical cancer, is clearly an unmet need. Intriguingly, treatment with the immune checkpoint inhibitor, nivolumab, in refractory metastatic squamous cell carcinoma of the anal canal (NCI9673) yielded initial proof of concept of the activity of immunotherapy against an HPV-associated malignancy, with an overall response rate of 24% (CR rate of 5%; PR rate of 19%) [Morris et al., ASCO 2016].

1.1.4 Merkel Cell Carcinoma

Merkel Cell Carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, with an estimate incidence of 1,500 new cases per year in the US, which is rising. Patients with metastatic disease have a 2-year survival of approximately 25%, representing a major unmet clinical need (Lemos et al., 2010). Currently, there is no FDA approved treatment for unresectable, recurrent, or metastatic MCC. Given it is a high-grade neuroendocrine carcinoma, patients are usually treated with chemotherapy regimens frequently used in small cell lung cancer [NCCN guidelines], however, responses are of short duration and the benefit of chemotherapy is questionable. MCC is associated with the Merkel cell polyomavirus in 40-100% of the cases (Feng et al., 2008, Rollison et al., 2010). The risk of developing MCC is increased from 5 to 50-fold in immunocompromised individuals, and there are reports of tumor regression following

improvement in immune system function(Bhatia et al., 2011). PD-L1 expression is seen in 49% of MCC and expression in tumor-infiltrating lymphocytes occurs in 55% of the patients (Lipson et al., 2013). Recently, encouraging activity has been reported with single agent anti-PD1 in this patient population (Nghiem et al., 2016). VEGF-A, VEGF-C and VEGFR2 overexpression is also prevalent in MCC and correlates with metastatic potential (Brunner et al., 2008, Kukko et al., 2007). Thus, there is significant rationale for pursuing dual VEGF and PD-L1 blockade.

1.1.5 Neuroendocrine tumors, pancreatic and extra pancreatic

Well-differentiated neuroendocrine tumors (NETs) are relatively rare malignancies of a diffuse neuroendocrine network with a variable clinical course, and median survival ranging from 24 months to over ten years(Yao et al., 2008). Because of differences in effective therapy, they are often classified as either pancreatic NETs (pNETs) or extra pancreatic NETs. The mTOR inhibitor everolimus and the somatostatin analogues lanreotide and octreotide are the only drugs approved for the oncologic management of gastrointestinal NETs (Caplin et al., 2014, Rinke et al., 2009). In contrast, chemotherapy is standard in pancreatic NETs (PNETs) (Moertel et al., 1980, Moertel et al., 1992, Kouvaraki et al., 2004), as is the somatostatin analogue lanreotide (Caplin et al., 2014) and targeted agents such as everolimus(Yao et al., 2010) and sunitinib (Raymond et al., 2011). pNETs remain life-limiting, and response rates are universally less than 10%. Additional therapies are therefore desperately lacking for NETs. Immunotherapy, such as with interferon, as well as anti-VEGF therapy with bevacizumab and sunitinib, have been investigational and standard therapies in the NET field for decades, but the two strategies have never been tested in combination.

1.1.6 Peritoneal mesothelioma

Malignant peritoneal mesothelioma (MPM) is a rare disease and constitutes about 10% of all cases of malignant mesothelioma.(Rodriguez et al., 2009) With an annual incidence of 1 per 100,000 population, approximately 300 – 400 cases are diagnosed in the United States every year.(Rodriguez et al., 2009) Current options for systemic therapy are limited and afford modest survival benefit.(Janne et al., 2005, Vogelzang et al., 2003) The standard of care for frontline unresectable MPM is platinum-pemetrexed.(Vogelzang et al., 2003, Janne et al., 2005) Beyond the first-line therapy, no good standard of care or FDA approved agents exist. Single agent gemcitabine and vinorelbine are used in the salvage setting due to modest activity seen in pleural mesothelioma (response rate 8-16%) and are riddled with toxicity.(van Meerbeeck et al., 1999, Stebbing et al., 2009) Historically, the progression-free survival (PFS) in this setting is about 1.7 months (Stebbing et al., 2009, van Meerbeeck et al., 1999) Therefore, there is an unmet and critical need to develop novel agents for this orphan disease. Tremelimumab, a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA4), has shown encouraging clinical activity and acceptable safety profile in refractory patients with malignant pleural mesothelioma with a disease control rate of 30% and a PFS of 6.2 months.(Calabro et al., 2013) The preliminary results of KEYNOTE-

028 trial with a cohort of patients (N = 25) with malignant pleural mesothelioma (AACR 2015) showed an ORR of 28% and SD in 48% patients.(Karim and Leighl, 2016) One of our patients with MPM treated with Atezo on protocol 2015-0239, who was refractory to cisplatin and pemetrexed received a major response at first restaging. Addition of bevacizumab to chemotherapy significantly improves OS in malignant mesothelioma and is currently being considered for regulatory approval (Zalcman et al., 2016). Furthermore, VEGF leads to a functional defect of the dendritic cells and decreased antigen presentation and inhibition with bevacizumab increases B and T cell compartments (Manzoni et al., 2010). Therefore combining two potentially active therapies with plausible synergistic effects could help antitumor efficacy of this combination in mesothelioma.

1.1.7 Pleural mesothelioma

Malignant mesothelioma (MM) is an orphan disease that is difficult to treat.(Tsao et al., 2009) Novel agents are critically needed as the median overall survival with advanced MM is 1 year and there are no FDA approved agents in the salvage setting. In the past year, The Intergroupe Francophone de Cancerologie Thoracique (IFCT) published their positive results on the Phase III MAPS trial which compared cisplatin-pemetrexed with and without bevacizumab. Both the PFS (HR 0.61, p<0.0001) and OS (HR 0.77, p=0.0167) were prolonged in the patients who received bevacizumab (Zalcman et al., 2015). This is the first triplet regimen with a novel biologic agent that has demonstrated a clear survival benefit to MM patients, and is undergoing evaluation for regulatory approval.

Programmed death 1 (PD1) protein, a T-cell co-inhibitory receptor, and one of its ligands PD-L1 are targets for immunotherapy. PD-1 receptor binds with PD-L1 and inhibits T-cell inhibition and downregulates T-cell responses. Inhibition of their interaction has been shown to lead to restoration of T-cell activity and a subsequent anti-tumor effect in several tumor types. There are several PD-L1 inhibitors under development; to name a few, BMS0936559 (Bristol-Meyers Squibb), MEDI-4736 (Medimmune), and atezolizumab (Genentech) (Brahmer et al., 2012, Brahmer et al., 2014, Davies, 2014). In non-small cell lung cancer, response rates ranging from 10% to 26% have been reported using these PD-L1 inhibitors as monotherapy in Phase I and II trials (Brahmer et al., 2014, Brahmer, 2013, Brahmer et al., 2012, Davies, 2014). MM is anticipated to be a highly immunogenic disease (Thomas and Hassan, 2012). At ESMO 2014, Mansfield et al. (Mansfield et al., 2014) reported a 40% PD-L1 IHC expression in pleural mesotheliomas (n=224) using a mouse monoclonal anti-human B7-H1 (clone 5H1-A3). PD-L1 IHC expression was associated with more disease burden and less offers of surgery to the patient. Also, PD-L1 IHC expression was associated with a worse survival 6 months vs 14 months, p<0.0001) (Mansfield et al., 2014). At AACR 2015, pembrolizumab was shown in 25 mesothelioma patients to have an overall response rate of 28% and 48% stable disease for a disease control rate of 76%. There were no new safety signals with this regimen.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al., 2016, Rosenberg et al., 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma or non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 BACKGROUND ON BEVACIZUMAB

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 22,000 patients and in multiple tumor types. Approximately 1,720,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab’s safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.66 ($p < 0.001$) and a median survival of 20.3 vs. 15.6 months. Similar increases were seen in progression-free survival (10.6 vs. 6.2 months; HR 0.54, $p < 0.001$), overall response rate (34.8% vs. 44.8%; $p = 0.004$) and duration of response (10.4 vs. 7.1 months; HR 0.62, $p = 0.001$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, November 2012). Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United

States for first-line treatment in combination with IV 5 FU−based chemotherapy for subjects with metastatic colorectal cancer.

Bevacizumab has also been approved based on additional Phase III trials in metastatic CRC (E3200 and ML18147) non−small cell lung cancer (NSCLC; E4599), and renal cell carcinoma (RCC; AVOREN) which also demonstrated clinical benefit from bevacizumab. Furthermore, Phase II studies in glioblastoma (GBM; AVF3708g and NCI-06-C0064) showed an improvement in objective response rate. These studies led to accelerated approval by the FDA for recurrent GBM.

In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated, Avastin naive metastatic CRC patients. In Study ML18147, bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy regimens demonstrated a statistically significant increase in OS compared to oxaliplatin- or irinotecan-based chemotherapy alone (11.2 vs. 9.8 months, respectively, HR = 0.81; p=0.0062) in metastatic CRC patients who had previously received bevacizumab as a part of their 1st line treatment (Bennouna et al., 2013). These two studies led to FDA approvals for bevacizumab for previously treated metastatic CRC patients, in 2006 and 2013, respectively.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; p = 0.003). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006.

In previously untreated metastatic RCC patients, bevacizumab in combination with interferon-alfa showed an improved progression free survival compared to interferon-alfa alone (10.2 vs. 5.4 months, respectively; HR=0.63; p=0.0001). These results supported the FDA approval of bevacizumab with interferon-alfa in metastatic RCC in July 2009.

Two Phase II trials investigated bevacizumab as a single agent in patients with recurrent GBM. In AVF3708g, patients with recurrent GBM were randomized to bevacizumab or bevacizumab plus irinotecan and demonstrated an improvement in objective response rate (28.2% vs. 37.8%, respectively). The NCI-06-C0064 study was single arm Phase II study in recurrent GBM patients treated with bevacizumab alone and showed an objective response rate of 19.6%. This study supported the results from AVF3708g, and based on the objective response rate in these two trials, the FDA granted accelerated approval for bevacizumab as a single agent in GBM patients with progressive disease following prior therapy. In 2013, results from two phase III randomized controlled trials for newly diagnosed GBM were presented, one Roche-sponsored trial (AVAglio) and one cooperative group trial (RTOG 0825). In AVAglio, progression free survival was

significantly longer with bevacizumab when added to radiation therapy/temozolomide (HR 0.64, mPFS 10.6 vs 6.2 months). Health-related quality of life (HRQoL) and Karnofsky performance score (KPS) were stable/improved during PFS (both arms). Patients receiving bevacizumab plus radiation therapy/temozolomide had diminished corticosteroid requirement, but reported more adverse events (AEs) compared with placebo plus radiation therapy/temozolomide (serious AEs: 36.6% vs 25.7%; grade ≥3: 62.7% vs 50.1%; grade ≥3 AEs of special interest to bevacizumab: 28.7% vs 15.2%). In RTOG 0825, PFS was extended for bevacizumab (7.3 vs.10.7 months, HR 0.79) but did not meet the pre-specified endpoint for significance. There was no difference between arms for overall survival (median 16.1 vs.15.7 months, HR 1.13).

Lastly, in the E2100 study, patients with untreated metastatic breast cancer who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively, HR 0.48; $p<0.0001$) and this led to the accelerated approval of bevacizumab in metastatic breast cancer. Unfortunately, the clinical benefit was not confirmed in subsequent trials and the FDA ultimately removed the label for the breast cancer indication. (See the Bevacizumab Investigator Brochure for additional details).

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite recent advances in the treatment of more common cancers, patients with rare solid tumors have seen slow progress in recent years. For the reasons specified in Section 1.1, each of the tumor types being investigated in this study has strong preclinical and/or clinical rationale for a study of checkpoint inhibition in combination with VEGF inhibition, and presents an unmet medical need in the metastatic setting. It is therefore imperative to explore the antitumor activity of this combination in these cohorts.

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Chen et al., 2012, Hodi et al., 2010, Kantoff et al., 2010).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al., 2005, Keir et al., 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007).

Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

In multiple murine tumor models, the interruption of the interaction between PD-L1 and PD-1 resulted in anti-tumor effects (Iwai et al. 2002; Strome et al. 2003). PD-L1 blockade in the syngeneic colorectal cancer model MC-38 (expressing the foreign antigen ovalbumin) resulted in complete responses in all test animals in fewer than 2 weeks of treatment (unpublished Roche data).

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. VEGF is believed to be involved in immune response via the induction of myeloid-derived suppressor cells (MDSCs). These VEGF-induced MDSCs can suppress both T-cell and dendritic-cell function (Gabrilovich 2012). Anti-VEGF therapies may elicit immune responses through diverse mechanisms, including increased trafficking of T cells into tumors (Manning et al. 2007; Shrimali et al. 2010), reduced frequency of MDSC (Kusmartsev et al. 2008), reduction of suppressive cytokines and tumor-infiltrating T regulatory cells and MDSCs (Roland et al. 2009), and increased CD8+ and CD4+ central memory T cells (Hodi et al. 2011).

Collectively, the role of VEGF in the immune response and its critical role in the pathogenesis of multiple malignancies, including several of those in this study, provide a compelling rationale to test whether inhibition of the PD-L1/PD-1 pathway with a human anti−PD-L1 IgG1 effector less antibody with anti-VEGF therapies will result in improved clinical benefit for patients with these diseases.

The safety profile and associated benefit and risk of atezolizumab as a single agent (Phase Ia Study PCD4989g) and in combination with bevacizumab (Phase Ib Study GP28328 and Phase II Study WO29074) support its continued development. In the Phase Ib study of atezolizumab + bevacizumab (Study GP28328), 1 treatment-related grade 3-5 adverse event was observed (Table 1), and the most commonly observed AEs were fatigue, nausea, and pyrexia (Table 2).

Table 1 All Reported Adverse Events in Bevacizumab + Atezolizumab Arm of Study GP28328

	No (%) of Adverse Events

Parameter	Total		Treatment-Related	
Any adverse event	35	(100.0)	27	(77.1)
Grade 3-5 adverse event	18	(51.4)	1	(2.9)
Serious adverse event	14	(40.0)	0	(0.0)
Adverse event leading to death (Grade 5)	1	(2.9)	0	(0.0)

Table 2 Reported Adverse Events in at least 10% of Patients in Bevacizumab + Atezolizumab Arm of Study GP28328

	No (%) of Adverse Events			
Preferred Term	Total		Treatment-Related	
Any adverse event	35	(100.0)	27	(77.1)
Fatigue	16	(45.7)	7	(20.0)
Nausea	13	(37.1)	7	(20.0)
Pyrexia	13	(37.1)	6	(17.1)
Diarrhea	11	(31.4)	8	(22.9)
Decreased appetite	9	(25.7)	5	(14.3)
Abdominal pain	7	(20)	0	(0.0)
Chills	7	(20.0)	4	(11.4)
Hypertension	7	(20.0)	0	(0.0)
Vomiting	7	(20.0)	2	(5.7)
Cough	6	(17.1)	3	(8.6)
Dyspnoea	6	(17.1)	2	(5.7)
Oedema peripheral	6	(17.1)	0	(0.0)
Upper respiratory tract infection	6	(17.1)	0	(0.0)

Anaemia	5 (14.3)	2 (5.7)
Anxiety	5 (14.3)	0 (0.0)
Epistaxis	5 (14.3)	1 (2.9)
Headache	5 (14.3)	0 (0.0)
Pain in extremity	5 (14.3)	1 (2.9)
Pneumonia	5 (14.3)	0 (0.0)
Pruritus	5 (14.3)	3 (8.6)
Rash	5 (14.3)	3 (8.6)
Arthralgia	4 (11.4)	1 (2.9)
Constipation	4 (11.4)	0 (0.0)
Insomnia	4 (11.4)	0 (0.0)
Productive cough	4 (11.4)	0 (0.0)
Bone pain	3 (8.6)	2 (5.7)
Musculoskeletal pain	3 (8.6)	1 (2.9)

This trial will enroll patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with bevacizumab is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab when given in combination with bevacizumab (atezo+bev) in patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. Specific objectives and corresponding endpoints for the study are outlined below.

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezo + bev	• Objective response (defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart as determined by a blinded independent radiologist according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of atezo + bev	• Objective response as determined by an independent radiologist according to immune-modified RECIST • PFS (defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first) as determined by an independent radiologist according to RECIST v1.1. • DOR (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first) as determined by an independent radiologist according to RECIST v1.1 • Disease control as determined by the independent radiology according to RECIST v1.1 • Overall survival, defined as the time from enrollment to death from any cause • PFS as determined by an independent radiologist according to immune-modified RECIST • DoR as determined by an independent radiologist according to immune-modified RECIST • Disease control as determined by the independent radiologist according to immune-modified RECIST
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of atezo + bev	• Occurrence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to atezo + bev (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to atezo + bev, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, or can increase the	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

knowledge and understanding of disease biology	

DOR = duration of response; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

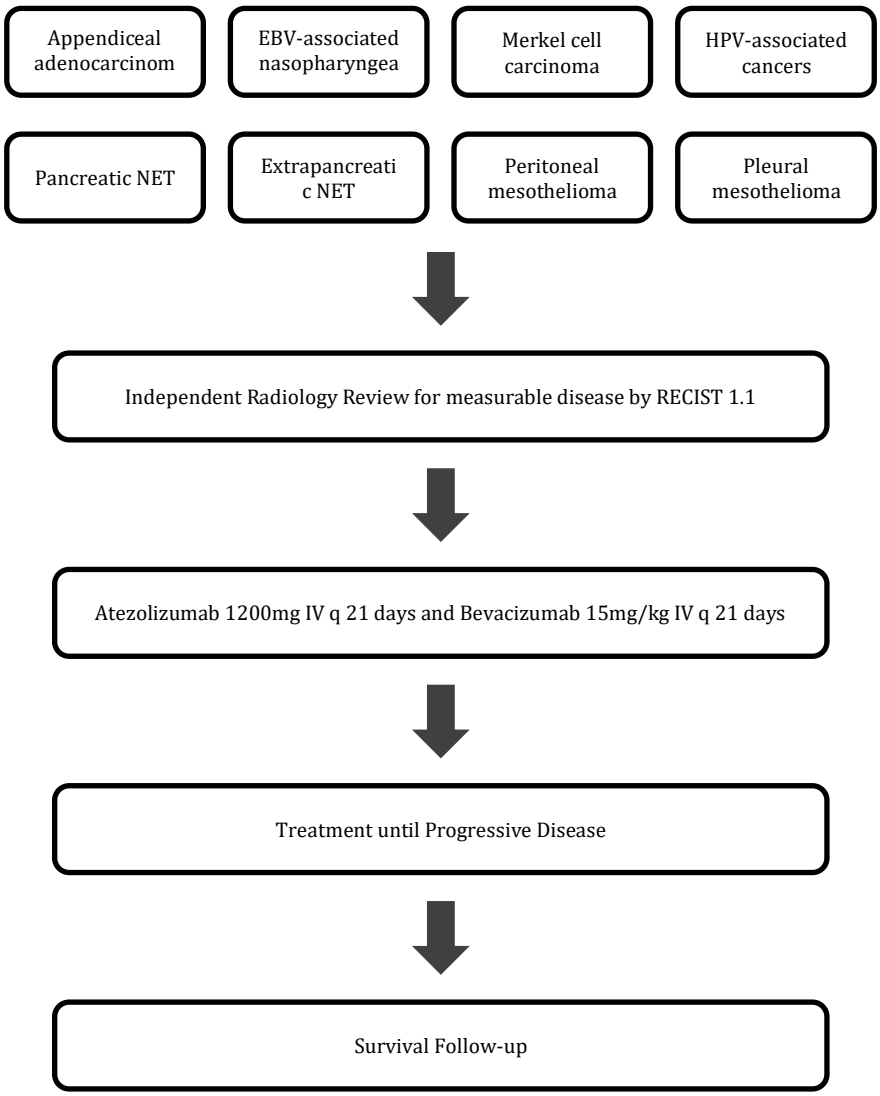
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This study will be a Phase II, single-center, single-arm, open label study evaluating the efficacy and safety of the combination of bevacizumab and atezolizumab in parallel cohorts of patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. The study will enroll approximately 160 patients, with 20 patients in each cohort.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV = intravenous; RECIST = Response Evaluation Criteria in Solid Tumors.

Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle and bevacizumab will be administered by intravenous (IV) infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue study treatment if they meet <u>all</u> of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients will undergo tumor assessments by independent radiology review at scheduled intervals during the study (see Section 4.5.5 and Appendix 1 for details).

The expected total length of time on study is anticipated to be approximately 15 months, with 2 weeks spent in screening, 4 weeks in washout, 12 months receiving therapy, and 2 months of follow-up prior to the final protocol visit.

Patients will undergo mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by the investigator, on cycle 2 days 1 and at the time of first evidence of radiographic disease progression according to RECIST v1.1 within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner. These samples will be analyzed to evaluate tumor-infiltrating immune cells [ICs]). In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, which is expected to be 2 months after the last dose of either agent is administered, given that both atezolizumab and bevacizumab have elimination half-lives of approximately 28 and 21 days, respectively. The end of the study is expected to occur approximately 14 months after the last patient is enrolled. In addition, the PI may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Primary and Secondary Endpoints

The primary endpoint of the study is objective response using RECIST 1.1. Each cohort will be assessed independently, given that each individual disease under study has a distinct natural history. Objective response has long been a standard endpoint in phase II studies seeking preliminary evidence of anti-tumor efficacy, and has been identified as predictive of phase III outcome across tumor types (Oxnard et al., 2016).

Secondary endpoints of PFS and OS are accepted assessments of treatment benefit across patient populations, and PFS will be measured using both RECIST 1.1 and irRECIST to permit both accurate reflection of immunotherapy activity and comparison to prior studies.

3.3.2 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) Q3W was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration–to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose. Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg).

3.3.3 Rationale for Patient Population

This study will enroll patients with advanced appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extra pancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma, regardless of PD-L1 expression.

Each of these advanced cancers remains incurable and life limiting. For nearly all of these tumor types, there is no FDA-approved therapy for the patient population being included in the study. The major exceptions are the neuroendocrine tumor cohorts, where FDA-approved therapy is available, but is frequently deferred in favor of clinical trials of promising agents in appropriately selected patients, given the overall need for

additional therapies. Therefore, there remains a continuing need for more efficacious, safe, and better-tolerated treatments for patients with these rare cancers. As discussed in section 1.1, each tumor type has strong preclinical and/or clinical rationale for studying combined PD-L1 and VEGF inhibition to match the unmet need for additional therapies.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 correlates with response to therapy in several, but not all tumor types (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016).

Atezolizumab monotherapy has demonstrated clinical efficacy and is generally well tolerated in patients with other malignancies (Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016). In a Phase II study (GO28753), patients with advanced NSCLC had a significant improvement in OS when treated with atezolizumab compared with docetaxel in the second- or third-line setting (Fehrenbacher et al. 2016).

3.3.4 Rationale for Evaluating Atezolizumab in these Patient Populations

Immune checkpoint inhibitors, including atezolizumab, have demonstrated the potential to deliver significant clinical benefit to patients with advanced cancer (see Section 1.2). In this respect, atezolizumab is an example of an agent that is well tolerated and has the potential to deliver an excellent therapeutic index. In addition, because these therapies have the potential to induce potent anti-tumor immunity, there exists the potential for long-term durable responses.

Each of the diseases under study has significant rationale for studying the impact of immunomodulation. In appendiceal adenocarcinoma, the significant genomic, morphologic, and immunologic similarities to colorectal adenocarcinoma, in which this combination has already shown promise in study GP28328 (NCT01633970). In EBV-associated nasopharyngeal carcinoma, PD-L1 expression and VEGF overexpression are nearly universal, with PD-L1 suppressing the response to EBV(Barber et al., 2006, Fang et al., 2014). PD-1/PD-L1 inhibition has already shown promise in treating HPV-associated squamous cell carcinoma of the anal canal (Morris et al., ASCO 2016), Merkel cell carcinoma(Nghiem et al., 2016), and mesothelioma(Karim and Leighl, 2016). In neuroendocrine tumors, VEGF inhibition and immunomodulation have both played important roles in the treatment of advanced disease, but the two strategies have never been combined.

3.3.5 Rationale for Evaluating Atezolizumab and Bevacizumab in combination

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggest that in the tumor

microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune-cell recruitment to the tumor site (Bouzin et al. 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaireddendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study of melanoma patients combining an immunomodulatory antibody (anti−CTLA-4; ipilimumab) and bevacizumab (Hodi et al. 2011). In this study of an immunomodulatory agent and bevacizumab, best overall responses were PR in 8 of 22 patients (35%) and stable disease in 6 of 22 patients (27%). All responses were durable for > 6 months. Therefore, the combined treatment with atezolizumab and bevacizumab may augment the antitumor immune response, resulting in improved and more durable clinical benefit.

3.3.6 Rationale for Open-Label Study

An open-label study design was chosen for this trial for a number of reasons. Given the known toxicities associated with immunotherapy, patients assigned to atezolizumab-containing arms, as well as physicians, may be capable of identifying treatment assignment in a blinded study. In addition, a blinded study would require prolonged administration of placebo, which could pose a significant burden to patients. Furthermore, because of the potential for pseudoprogression in patients randomized to atezolizumab-containing arms, a blinded study would require all patients to continue treatment until loss of clinical benefit regardless of whether they were receiving atezolizumab. This could then delay subsequent treatment with approved therapies in patients assigned to the control arm, as well as increase the complexity of treatment decisions.

To ensure the validity of data collected in an open-label study, efficacy analyses will include a supportive analysis based on IRF assessment of progression. In addition, the strategy and timing for final analysis of the primary endpoint, including censoring rules and methods for handling missing data, have been pre-specified in the protocol.

3.3.7 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions

or areas of new growth in existing lesions revealed ICs and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients to continue treatment after apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.1). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status.

3.3.8 Rationale for the Use of Immune-Modified RECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix 4). It is required that radiographic progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression (caused by immune cell infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, use of immune-modified RECIST will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit.

3.3.9 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, after 3 weeks of therapy and at the time of first evidence of radiographic disease progression to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by immune cell infiltration) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T-cell activation, circulating tumor DNA (ctDNA) concentration, and lymphocyte subpopulations may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible, tumor tissue collected at 3 weeks of therapy and at the time of progression will enable NGS and RNA profliing to identify germline and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 160 patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extra pancreatic neuroendocrine tumors, peritoneal mesothelioma, and peritoneal mesothelioma (20 patients per diagnosis) will be enrolled in this study.

4.1.1 Inclusion Criteria

4.1.1.1 Basket-specific Inclusion Criteria

1. Appendiceal adenocarcinoma
    a. Metastatic appendiceal adenocarcinoma
    b. Not considered candidate for curative surgery

2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. EBV positive by EBV encoded small RNA in situ hybridization (EBER ISH)
    c. Any number of prior therapies, including 0

3. Human Papilloma Virus-associated cancers
    a. Histologically proven squamous carcinoma of the anal canal, penile, vaginal, vulva, or cervical cancer that has progressed after at least one treatment regimen including cisplatin or carboplatin will be enrolled. HPV confirmation is not required.
    b. Patients must have metastatic disease not amenable to surgical resection.
    c. If HIV+ positive, all patients infected with Human Immunodeficiency Virus (HIV) and CD4+ T cell count > 400 cells/mm^3 may be eligible for study.
    d. Patients co-infected with hepatitis B virus and/or hepatitis C virus may be included in this study provided that their liver function tests remain within the limits listed above. Patients must be followed by a hepatologist during the course of this study.

4. Merkel Cell Carcinoma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Any number of prior therapies, including 0

5. Neuroendocrine tumors, pancreatic
    a. Grade 1 or grade 2 according to reviewing pathologist
    b. Progressive disease over the preceding 12 months
    c. Any number of prior therapies, including 0
    d. Patients using a somatostatin analogue for symptom control must be on stable doses for 56 days prior to enrollment.

6. Neuroendocrine tumors, extra pancreatic
    a. Grade 1 or grade 2 according to reviewing pathologist
    b. Progressive disease over the preceding 12 months
    c. Any number of prior therapies, including 0
    d. Patients using a somatostatin analogue for symptom control must be on stable doses for 56 days prior to enrollment.

7. Peritoneal mesothelioma
    a. Refractory to platinum and pemetrexed systemic therapy
    b. Not considered candidate for curative surgery

8. Pleural mesothelioma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Refractory to platinum and pemetrexed systemic therapy
    c. Any number of prior therapies

4.1.1.2 General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease according to RECIST v1.1

Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- ECOG Performance Status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L without transfusion
  - WBC Count $\geq$ 2500/ul
  - Hemoglobin ≥ 90 g/L

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN
  - Serum albumin ≥ 2.5 g/dL
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the last dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Basket-specific Exclusion Criteria

1. Appendiceal adenocarcinoma
    a. Complete or partial bowel obstruction
2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
    a. none
3. Human Papilloma Virus-associated cancers
    a. None
4. Merkel Cell Carcinoma
    a. none
4. Neuroendocrine tumors, pancreatic
    a. Grade 3, poorly differentiated neuroendocrine carcinoma
    b. Large cell or small cell histology
5. Neuroendocrine tumors, extrapancreatic
    a. Grade 3, poorly differentiated neuroendocrine carcinoma
    b. Large cell or small cell histology
6. Peritoneal mesothelioma
    a. None
7. Pleural mesothelioma
    a. None

4.1.2.2 General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment for the studied cancer within 28 days prior to initiation of study treatment}
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the bevacizumab formulation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 5 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

    Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

    Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover < 10% of body surface area
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive HIV test at screening (except in cohort 3, HPV-associated cancers)
- Except in cohort 3, HPV-associated cancers, active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test and negative HBV DNA test at screening, are eligible for the study.
- Except in cohort 3, HPV-associated cancers active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study, or up to 5 months following the anticipated last dose of atezolizumab.
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

  Patients who received low-dose immunosuppressant medication are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg).

  Anti-hypertensive therapy to maintain a systolic blood pressure <150 mmHg and/or diastolic blood pressure < 100 mmHg is permitted.

- Prior history of hypertensive crisis or hypertensive encephalopathy
- History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
- Patients with a baseline ECG demonstrating a QTc > 460 ms
- Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 calendar days prior to Cycle 1, Day 1) use of dipyramidole, ticlopidine, clopidogrel, or cilostazol.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
- Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection

  All patients with $\geqslant$ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Treatment with the combination of atezolizumab and bevacizumab will be administered to all patients in an open-label, unblinded fashion. Patients will be assigned to cohorts based on tumor histology as assessed by an MD Anderson Cancer Center pathologist.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

Atezolizumab will be supplied by Genentech Inc as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

Atezolizumab may be prepared, handled, and administered per the current FDA-approved package insert.

4.3.1.2 Bevacizumab

Bevacizumab will be supplied by the Genentech Inc of Basel, Switzerland as a clear-to-slightly-opalescent, sterile liquid ready for parenteral administration. Each 400-mg (25-mg/mL) glass vial contains 16 mL of bevacizumab (25 mg/mL) with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only. For further details, see the Bevacizumab Investigator's Brochure.

Bevacizumab is intended for use solely in clinical trials. The drug provided for clinical trial use is expected to be very similar in safety and activity to the commercially marketed drug (Avastin®).

Bevacizumab may be prepared, handled, and administered per the current FDA-approved package insert.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of any of the study treatments should be noted on the electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Atezolizumab will be administered prior to bevacizumab, with a minimum of 5 minutes between dosing.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±5) minutes after the infusion.

Refer to the FDA-approved package inserts for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.3 and in the Atezolizumab Investigator's Brochure.

4.3.2.2 Bevacizumab

The dose of bevacizumab in this study is 15 mg/kg administered by IV infusion every 3 weeks on Day 1 each 21-day cycle. The interval between infusions must not be < 10 days. The bevacizumab dose will be based on the patient’s weight at enrollment and will remain the same throughout the study unless there is a weight change of > 10% from baseline. It is not necessary to correct dosing based on ideal weight, unless warranted per institutional guidelines/standard.

The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The

patient should be observed for at least 2 hours after the first administration of the combination and for at least 1 hour for subsequent infusions.

If a patient experiences an infusion-associated adverse event, he or she may be pre-medicated for the next bevacizumab infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes as long as the patient continues to be pre-medicated. If a patient experiences a second episode of an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 (± 15) minutes. Similarly, if a patient experiences a second episode of an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 (± 10) minutes.

Upon receipt of the bevacizumab, vials are to be refrigerated at 2°C−8°C (36°F−46°F) and should remain refrigerated until use. Vials should be protected from light. DO NOT FREEZE. DO NOT SHAKE. VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab and bevacizumab) will be provided by the Genentech Inc where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Genentech Inc with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Genentech Inc. The site must obtain written authorization from the Genentech Inc before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded in the electronic medical record.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 6).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, except as outlined below.

  After Cycle 1, Day 14, palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and bevacizumab may be continued during palliative radiotherapy.

  Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Re-screening is required if a patient has not met all of the eligibility criteria within 28 days from the original date of the screening visit. Re-screening refers to repeating the entire screening process with the exception of performing a repeat biopsy to collect a tumor tissue sample to be used to determine PD-L1 status and repeating CT and/or MRI imaging scans used for tumor assessment, provided the biopsy tissue sample and imaging scans were obtained during the original screening visit. Patients are only allowed to be re-screened twice. Blood samples may be redrawn due to sample handling problems, breakage, or sample integrity, without being considered a re-screen.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the

cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Height will be assessed at baseline, and weight will be assessed at each study visit.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and every 9-12 weeks thereafter (with neuroendocrine cohorts 5 and 6 assessed every 12 weeks and all other cohorts assessed every 9 weeks), regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for atezolizumab-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Cross sectional imaging will be performed with either contrast enhanced CT or MRI. RECIST 1.1 criteria will be used to determine disease response.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Response will be assessed by an independent, blinded radiologist at the MD Anderson Quantitative Imaging Analysis Core using RECIST v1.1 (see Appendix 3) and immune-modified RECIST (see Appendix 4). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Genentech Inc for analysis:

- Blood samples for exploratory research on biomarkers
- Fresh tumor tissue sample collected at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

  Tissue should be collected by excisional or core needle biopsy, typically using a 21-18 gauge needle. The biopsy should include at least 5 cores, 2 FFPE and 3 fresh frozen. It should be collected within 28 days prior to initiation of protocol therapy.
- Tumor tissue sample collected at week 3 and at time of progression for exploratory research on biomarkers

  Biopsies at week 3 should be performed within 7 days before or after the administration of C2D1 of study therapy. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, immunohistochemistry for PD-L1, multiplexed immunofluorescence for immune markers, flow cytometry, analysis of ctDNA concentration, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of germline or somatic mutations, and use of WGS or NGS.

For the neuroendocrine tumor cohorts, exploratory biomarkers will also include antibody titers to GAD and IA-2, assessed at baseline and after 3 weeks of treatment.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final manuscript has been completed, with the following exceptions:

- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Blood, plasma, serum, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final manuscript has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to patients unless required by law.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible.

Patients receiving bevacizumab should be carefully monitored for clinical signs and symptoms of congestive heart failure, especially in patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF should also be considered (echocardiogram or MUGA).

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Mandatory Samples for Whole Genome Sequencing

Blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) to identify germline or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research and the WGS portion of the Informed Consent Form by the Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored

in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from WGS specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Genentech, Inc. policy on study data publication.

4.5.8.1 Guidelines for Return of Incidental Results:

The decision-making for return of incidental results will be made as approved by the MD Anderson Cancer Center IRB in protocol PA12-1099 and described herein: Return of incidental results guidelines are being generated for common genetic alterations by a Return of Results Committee via Consultation between Institute of Personalized Cancer Therapy, Clinical Cancer Genetics, Molecular Diagnostic Laboratory, and Behavioral Science. Rarer alterations will be discussed on a case by case basis by the Return of Results Committee with input from Clinical Cancer Genetics, and selected cases will be discussed in person or virtually in the Molecular Tumor Board. The treating investigator will initiate return of results with genetic counseling based on recommendations of the Return of Results Committee. We will be initially reporting cancer-related genes only and only those that are clearly deleterious and actionable; we will expand our reporting to non-cancer related risk genes as we establish expertise in genetic counseling in this arena. This reporting will be congruent with the IRB-approved guidance for reporting of such results.

Patients with deleterious germline alterations who are alive but not under MD Anderson care will be contacted by treating investigator after discussion of the alteration in return of results committee and validation of the alteration in an anonymized fashion.

Genetic alterations will be considered to have “clinical utility” if the genetic risk associated with the variant is well-recognized and significant. Variants for which there would be clinical implications such as change in screening, chemoprevention or other behavior change, change in therapy or drug dose will be considered to have clinical utility. Variants that confer a high disease risk and that can be reduced by prevention/therapy would be especially prioritized for return.

We will initially consider return of results on cancer-related genes felt to have clinical utility. Please refer to protocol PA12-1099 for genes that are currently tested by our clinical cancer genetics program, as well as other cancer-related genes that may have clinical utility. These genes will be prioritized for discussion in the Return of Results Committee, and alterations in these genes will be specifically considered for return to patients with appropriate genetic counseling and CLIA validation. Notably, the actionability or clinical utility of any particular variant within a gene will also depend upon the pathogenicity of that variant as determined by the lab’s interpretation (e.g. polymorphism, low-penetrance susceptibility, variant of unknown significance, deleterious mutation associated with hereditary cancer). Examples of this include germline MET T1010I vs. MET mutations causative of hereditary papillary renal cancer, and APC I1307K vs. APC mutations causing FAP.

If an alteration is determined to have clinical utility based on guidelines developed, or based on assessment by the Return of Results Committee and/or by Clinical Cancer Genetics or by discussion at Molecular Tumor Board, next the alteration would be validated in a CLIA validated laboratory, in anonymized fashion, when possible. For cancer-related genes, this testing will be done using a unique “study identifier” rather than “patient identifiers” to protect the patient’s privacy. The testing may be outsourced to Medical Genetics Laboratories at Baylor, Myriad Genetics Illumina, Invitrae, Ambry, Guardant, Genomic Health, Broad Institute, Life Technologies/ThermoFisher, Complete Genomics etc. If MD Anderson develops CLIA tests for these alterations in the future, they may be done at MD Anderson. After confirmation of the alteration in a CLIA lab, patient will be contacted. The testing may identify conditions for which genetic counseling and germline testing in the CLIA environment is frequently facilitated in our institution (e.g. BRCA testing). If sample is not available for validation in a CLIA lab, results felt to be deleterious and high confidence as assessed by the Return of Incidental Results Committee may be returned to the patient without additional testing. Notably, to date all deleterious germline validations identified were successfully validated on a separate CLIA assay. For these alterations, the patient will be contacted by the treating investigator or genetic counselor, and invited for formal genetic counseling. Standard clinical counseling and CLIA testing will then be recommended for at-risk family members. Of note, in some unfortunate cases the patient may be deceased when the results of genomic testing become available, and the patient’s designated power of attorney will be contacted instead.

Return of incidental results to patients by the investigator or clinical cancer genetics team will be documented either with a telephone note or a clinic note.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab and bevacizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per RECIST v1.1, with the following exception:

  Atezolizumab-treated patients will be permitted to continue study treatment after experiencing radiographic disease progression per RECIST v1.1 if they meet all of the following criteria:

  – Evidence of clinical benefit, as determined by the investigator following a review of all available data
  – Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
  – Absence of decline in ECOG Performance Status that can be attributed to disease progression
  – Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit $\leq$30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of

clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or Genentech, Inc. terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination
- Patient non-adherence to the study plan as determined by the investigator

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The PI has the right to terminate this study and one or more cohorts in the study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1 and 5.1.2). Guidelines for management of patients who experience specific adverse events are provided in Table 5 (see Section 5.1.3.3).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate

equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs, immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis. In addition, systemic immune activation (described below) is a potential risk associated with atezolizumab. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the PI for additional recommendations.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: hypertension, proteinuria, venous thromboembolism, arterial thromboembolism, gastrointestinal perforation, fistula, wound healing complications, hemorrhage, mucocutaneous hemorrhage, posterior reversible leukoencephalopathy, systolic heart failure, ovarian failure, neutropenia, and hypersensitivity and infusion reactions. Please refer to section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The bevacizumab dose will be based on the patient's weight at enrollment and will remain the same throughout the study, unless there is a weight change of > 10% from baseline. It is not necessary to correct dosing on the basis of ideal weight, unless warranted per institutional guidelines/standard. Management of bevacizumab may be performed according to the label.

5.1.3.2 Treatment Interruption

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >105 days, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >105 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Patients who discontinue atezolizumab either transiently or permanently (e.g., for adverse events) may continue on bevacizumab until disease progression if there is felt to be clinical benefit.

Patients who discontinue bevacizumab transiently or permanently for adverse events may continue on single-agent atezolizumab until disease progression if there is felt to be clinical benefit. Patients with Grade ≥ 3 toxicities attributable to bevacizumab should withhold atezolizumab until those toxicities have improved to Grade ≤ 2 (exception for Grade 3 hypertension). If bevacizumab is permanently discontinued but there is felt to be clinical benefit from atezolizumab, the latter may be continued.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. Patients who develop Grade 4 toxicities related to bevacizumab for > 21 days should permanently discontinue bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be

withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab should occur ≥ 28 days after surgery and after wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

Bevacizumab infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

5.1.3.3 Management Guidelines

Guidelines for management of patients who experience specific adverse events are provided in Table 5.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Atezolizumab:	
Anaphylaxis	• For anaphylaxis precautions, see Appendix 6.
IRRs	
Atezolizumab infusion-related reaction, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Interrupt or slow the rate of atezolizumab infusion • Continue bevacizumab.
Atezolizumab infusion-related reaction, Grade 3 or 4	• Permanently discontinue atezolizumab • Continue bevacizumab
Pulmonary events	
Pneumonitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.

Event	Action to Be Taken
Pneumonitis, Grade 2	• Hold atezolizumab until resolution • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. If not, permanently discontinue bevacizumab. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Pneumonitis, Grade 3 or 4	• Permanently discontinue atezolizumab • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper. • Permanently discontinue bevacizumab.
Hepatotoxicity	
Immune-mediated hepatitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Immune-mediated hepatitis, Grade 2	• Hold atezolizumab until resolution • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper, for grade 2 elevation of transaminases, with or without bilirubin elevation. **Events of > 5 days' duration:** • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Immune-mediated hepatitis, Grade 3 or 4	• Permanently discontinue atezolizumab • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper • Permanently discontinue bevacizumab.
Hepatic event, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Hepatic event, Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. **Events of > 5 days' duration:** • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Hepatic event, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.

Event	Action to Be Taken
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Diarrhea or colitis, Grade 2	• Hold atezolizumab • If symptoms persist for longer than 5 days or recur, administer 1-2mg/mg/day prednisone equivalent • When symptoms resolve to Grade 0 or 1, taper corticosteroids over at least 1 month • Resume treatment with atezolizumab if the event resolves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg/day oral prednisone or less. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diarrhea or colitis, Grade 3	• Hold atezolizumab • Administer 1-2mg/mg/day IV methylprednisolone • When symptoms resolve to Grade 0 or 1, taper corticosteroids over at least 1 month • Resume treatment with atezolizumab if the event resolves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg/day oral prednisone or less. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Endocrine disorders	
Hypophysitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab
Hypophysitis, Grade 2 or 3	• Withhold atezolizumab • Administer corticosteroids and hormone replacement as clinically indicated • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.

Event	Action to Be Taken
Hypophysitis, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Asymptomatic hypothyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Symptomatic hypothyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab and begin thyroid replacement therapy as needed • Isolated hypothyroidism should be managed with replacement therapy and without corticosteroids • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Withhold bevacizumab. • Resume bevacizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab and initiate an anti-thyroid drug as indicated. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Withhold bevacizumab. • Resume bevacizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue bevacizumab for life-threatening immune-related hyperthyroidism.

Event	Action to Be Taken
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once symptoms resolve. • Taper corticosteroids over at least 1 months when symptoms improve to Grade 0 or 1. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone, and the patient is stable on replacement therapy. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diabetes Mellitus, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Initiate treatment with insulin for type I diabetes mellitus • Continue bevacizumab.
Diabetes Mellitus, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Resume atezolizumab when metabolic control is achieved on insulin replacement therapy. • Withhold bevacizumab. • Resume bevacizumab when symptoms resolve and glucose levels are stable.
Ocular toxicity	
Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.

Event	Action to Be Taken
Pancreatic toxicity	
Amylase and/or lipase elevation, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Amylase or lipase elevation, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks, and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue bevacizumab.
Immune-related pancreatitis, Grade 2 or 3	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue bevacizumab.
Immune-related pancreatitis, Grade 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Recurrent pancreatitis of any grade is to be considered a grade 4 event. • Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Infection	

Event	Action to Be Taken
Infection, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Follow guidelines provided in the Bevacizumab Package Insert and Investigator's Brochure.
Infection, Grade 3	• Withhold atezolizumab • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. • Withhold bevacizumab • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Infection, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Dermatologic toxicity	
Rash, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Rash, Grade 3	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Rash, Grade 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.
Neurologic disorders	
Immune-related neuropathy, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.

Event	Action to Be Taken
Immune-related neuropathy, Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Institute medical intervention as appropriate • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks
Immune-related neuropathy, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Institute medical intervention as appropriate • Permanently discontinue bevacizumab.
Myasthenia gravis and Guillain-Barré, all grades	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Institute medical intervention as appropriate • Consider initiation of systemic corticosteroids at a dose of 1-2mg/kg/day oral prednisone. • Permanently discontinue bevacizumab.
Immune-related meningitis or encephalitis, all grades	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves. • Taper corticosteroids over at least 1 months when symptoms improve to Grade 0 or 1. • Permanently discontinue bevacizumab.
Bevacizumab: **Hypertension**	
Grade 1	No dose modification
Grade 2	• Withhold bevacizumab. Start antihypertensive therapy per institutional policy. Patient may resume bevacizumab after blood pressure < 150/90 mmHg.

Event	Action to Be Taken
Grade 3	• Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	• Discontinue bevacizumab
Hemorrhage	
Grade 1 or 2, non-CNS, non-pulmonary events	• No bevacizumab modification
Grade 3 non-CNS, non-pulmonary events	• Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. • Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab.
Grade 4 non-CNS, non-pulmonary events	• Discontinue bevacizumab
Grade 1 pulmonary events	• Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary events	• Discontinue bevacizumab
CNS hemorrhage, any grade	• Permanently discontinue bevacizumab
Venous thromboembolism	
Grade 1 or 2	• No bevacizumab modification

Event	Action to Be Taken
Grade 3 or asymptomatic Grade 4	• If the planned duration of full-dose anticoagulation is < 2 weeks bevacizumab should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	• Discontinue bevacizumab
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	• Discontinue bevacizumab permanently.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
Grade 1 or 2	• No bevacizumab modification
Grade 3	• Withhold bevacizumab until resolution to Grade $\leqslant$ 1.
Grade 4	• Discontinue bevacizumab.
Proteinuria	
Grade 1 (urine dipstick 1^+ or urine collection 0.15 to 1.0 g/24 hr)	• No bevacizumab modification
Grade 2 (urine dipstick 2^+-3^+ or urine collection >1.0 to to 3.5 g/24 hr)	• For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose. • For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab. • Withhold bevacizumab for proteinuria > 2 g/24hr and resume when proteinuria is $\leqslant$ 2 g/24hr.
Grade 3 (urine dipstick 4^+ or urine collection > 3.5 g/24 hr)	• Withhold bevacizumab. • Resume bevacizumab when proteinuria $\leqslant$ 2g/24h[a]
Grade 4 (nephrotic syndrome)	• Discontinue bevacizumab.
GI Perforation	
Any grade	• Discontinue bevacizumab.
Fistula	
Any grade tracheoesophageal fistula	• Discontinue bevacizumab.

Event	Action to Be Taken
Grade 4 fistula (other than tracheoesophegeal)	• Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	• Continue bevacizumab for partial obstruction not requiring medical intevervention.
Grade ⩾ 2	• Discontinue bevacizumab.
Wound Dehiscence	
Any grade	• Discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy	
Any grade	• Discontinue bevacizumab.

IRR = infusion-related reaction; TSH = thyroid-stimulating hormone.

[a] All proteinuria values are from 24-hour urine collections

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor and to Genentech Inc, as outlined in Section 5.4.

5.2.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Genentech Inc products, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Adverse events may occur during the course of the use of Genentech Inc products in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events (regardless of grade or attribution) that occur after the consent form is signed but before treatment initiation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment initiation through 90 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 5.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to Genentech Inc)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical

recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Adverse Events of Special Interest (Immediately Reportable to the Sponsor and Genentech Inc)

Adverse events of special interest are required to be reported by the investigator to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7) and based on the following observations:
  - Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
  - Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Atezolizumab AEs of Special Interest:

- Pneumonitis
- Colitis

- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism or hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)

Bevacizumab AEs of Special Interest

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (or RPLS; any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

5.2.3 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Immune-mediated adverse events, including conditions (regardless of grade) suggestive of an autoimmune disorder, such as Grade ≥ 3 rash or pruritus, Grade ≥ 3 diarrhea or Grade ≥ 2 colitis.

Cases of potential drug-induced liver injury that include Grade ≥ 3 asymptomatic AST/ALT/total bilirubin elevations, or Grade ≥ 2 AST/ALT/total bilirubin elevations with constitutional symptoms (Hy's law, see Section 5.3.5.6)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor and Genentech Inc in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events (all grades and attributions), whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The PI or designee will be responsible for assigning attribution of adverse events to the study agent.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the

date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the underlying malignancy should be recorded on the eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor and Genentech Inc (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical

concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Deaths that occur after the adverse eventreporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Underlying Malignancy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR AND GENENTECH INC

Certain events require immediate reporting to allow the Sponsor and Genentech Inc to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor and Genentech Inc immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor and Genentech Inc within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (see Section 5.4.1 for further details)
- Adverse events of special interest (see Section 5.4.1 for further details)
- Pregnancies (see Section 5.4.2 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.1.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment (or until initiation of new systemic anti-cancer therapy, whichever occurs first). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$90 days after the last dose of study treatment are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by

scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.2.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

5.4.2.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.2.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Supporter Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, Genentech Inc or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The PI or designee will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the PI or designee will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Bevacizumab Investigator's Brochure

The PI or designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a phase II study to assess the efficacy of atezolizumab combined with bevacizumab in 8 rare solid tumor groups:

1. Appendiceal adenocarcinoma, KRAS-wild type
2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
3. Human Papilloma Virus-associated cancers
4. Merkel cell carcinoma
5. Neuroendocrine tumors, pancreatic
6. Neuroendocrine tumors, extrapancreatic
7. Peritoneal mesothelioma
8. Pleural mesothelioma

The primary endpoint is the overall best response since the start of the treatment. A total of 160 patients will be enrolled, i.e., 20 patients in each tumor group. Considering the rarity of the diseases, the patient accrual rate is approximately 1 to 2 patients per month per tumor group. And the total duration of the study will be up to 30 months.

6.1 DETERMINATION OF SAMPLE SIZE

For each tumor group, we will estimate the best response rate and its 95% confidence interval (CI). When the sample size is 20, and the response rate is 0.3, the two-sided 95% exact confidence interval using the Clopper and Pearson method will be (0.119, 0.543). The exact 95% CI is calculated for various scenarios of true best response rate in Table 9.

Table 8 The exact 95% CI is calculated for various scenarios of true best response rate

Sample Size (N)	Best response rate	95% exact CI
20	0.3	(0.119, 0.543)
20	0.2	(0.057, 0.437)
20	0.1	(0.012, 0.317)

The table below lists the response rate p_0 based on the historical data for each group.

Table 9 The best response rate based on historical data

	Tumor Type	p_0
1	Appendiceal adenocarcinoma, KRAS-wild type	1%
2	Epstein-Barr Virus-associated nasopharyngeal carcinoma	10%
3	Human Papilloma Virus-associated cancers	5%
4	Merkel cell carcinoma	5%
5	Neuroendocrine tumors, pancreatic	10%
6	Neuroendocrine tumors, extrapancreatic	5%
7	Peritoneal mesothelioma	1%
8	Pleural mesothelioma	5%

6.2 SUMMARIES OF CONDUCT OF STUDY

This is a basket trial of eight parallel phase II trials of the combination of Atezolizumab and Bevacizumab in rare cancer patients. Enrollment, study drug administration, and discontinuation from the study will be summarized by all patients and tumor group. The reasons for study drug discontinuation will be also tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by tumor group.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographic information (e.g. age, gender) at baseline will be analyzed, with data summarized in mean ± standard deviation, median and range for continuous variables, and in frequency count and percentage for categorical variables. The student t-test or the Wilcoxon test may be used to compare continuous variables among different tumor patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all patients who received at least one dose of the study drug.

6.4.1 Primary Efficacy Endpoint

The primary outcome is the overall best response rate (PR or CR) since the start of treatment, with the primary analysis performed no less than six months after the final patient is enrolled. For each tumor group, we will estimate the best response rate and its

95% exact confidence interval using the Clopper and Pearson method. And we will assess the efficacy of the combination treatment by performing the independent binomial test comparing the best response rate versus the historical control for each tumor group. Considering the limited sample size for each tumor group, we may apply the Bayesian classification and information sharing method proposed by Lee and Chen (submitted) in the data analysis. It will provide a more efficient and more powerful way to estimate and test the response rate for similarly performed groups. We will first cluster the tumor groups according to their response rate into the low- or high-response cluster first, and then apply the Bayesian hierarchical model to borrow information among groups within the same cluster in estimating their response rate and comparing it to the historical control.

6.4.2 Secondary Efficacy Endpoints

For each tumor group, median DOR and corresponding 2-sided 95% CI will be reported.

Time-to-event outcomes, including progression free survival (PFS) and overall survival (OS), will be estimated using Kaplan-Meier method. Patients discontinuing treatment for reasons other than toxicity (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination, or death, whichever occurs first. Patients who discontinue study treatment for reasons other than withdrawal of consent will be followed for survival and subsequent ant-cancer therapies approximately every 3 months until death, loss to follow–up, withdrawal of consent, or study termination. During this period, documentation of anti-cancer therapies should include administration start and stop dates. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model may be utilized to include multiple covariates in the time-to-event analysis.

6.4.3 Exploratory Efficacy Endpoints

Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each tumor group. The time-course of biomarker measures will be investigated graphically. If there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic regression will be used to explore possible associations between biomarker measures and clinical outcomes.

6.5 SAFETY ANALYSES

The safety analyses will include all patients who received at least one dose of study treatment, with patients grouped according to treatment received.

Verbatim adverse events and severity will be graded according to NCI CTCAE v4.0.

The safety analyses will include all patients who received at least one dose of study treatment. Toxicity data will be summarized by frequency tables for each tumor type group. The association between the types and severity of toxicity and the tumor group will be evaluated. No formal statistical testing will be performed on these summaries.

6.6 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with treatment response, including efficacy and/or adverse events. Biomarker analyses may be reported in a separate report.

6.7 INTERIM ANALYSES

6.7.1 Interim Safety Monitoring

For patient safety, A Bayesian toxicity monitoring rule will be implemented for the treatment related toxicity events during the duration of the treatment in all treated patients across 8 tumor groups.

A toxicity event is defined as:

---All non-hematologic AEs Grade $\geqslant$ 3 with the exceptions of:

- Grade 3 Nausea
- Grade ≥ 3 Diarrhea if reversible within 48 hours with maximal supportive care
- Electrolyte abnormalities that are reversible within 72 hours with supportive care and/or supplementation

---All hematologic AEs Grade $\geqslant$ 4

---Pneumonitis
---Colitis
---Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism or hypophysitis
---Hepatitis, defined as AST or ALT $>10\times$ ULN
---Systemic lupus erythematosus
---Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
---Hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation
---Nephritis
---Ocular toxicities (e.g. uveitis, retinitis)
---Myositis
---Myopathies, including rhabdomyolysis
---Grade $\geq$2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
---GI perforation, abscesses and fistulae (any grade)
---CNS bleeding
---Haemoptysis ≥ grade 2
---Arterial thromboembolic events (any grade)
---PRES (or RPLS; any grade)
---Non-GI fistula or abscess ≥ grade 2

Let p.tox be the toxicity probability, then if Pr [p. tox > 0.3] >0.9, we will terminate the study early. The protocol statistician will apply the monitoring every 5 patients for the first 20 patients, then every 10 for the rest of study. That is, we will early stop the study if we observe [# patients experiencing toxicity] / [#patients being treated] >= 4/5, 6/10, 8/15, 9/20, 13/30, 16/40, 20/50, 23/60, 27/70, 30/80, 33/90, 37/100, 40/110, 43/120, 46/130, 50/140, 53/150, or 56/160. The operating characteristic for applying this toxicity monitoring rule is shown in the table below.

Table 10 Operating characteristics for toxicity early stopping based 5000 simulation runs per scenario

True toxicity probability	Early stopping probability	Average sample size
0.2	0.021	157.0
0.3	0.317	123.8
0.4	0.950	47.1
0.5	0.999	19.1

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The University of Texas MD Anderson Cancer Center will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. The PI will perform oversight of the data management of this study.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at The University of Texas MD Anderson Cancer Center and records retention for the study data will be consistent with The University of Texas MD Anderson Cancer Center's standard procedures, which mandate that data be maintained indefinitely.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of the MD Anderson Cancer Center Prometheus EDC system.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

SAE data will be captured via eSAE in accordance with Sponsor policy.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the

Principal Investigator indefinitely, in accordance with the current policy of the MD Anderson Cancer Center IND office.

Written notification should be provided to the Sponsor and Genentech Inc prior to transferring any records to another party or moving them to another location.

7.6 MONITORING

During the study, a study monitor from the University of Texas MD Anderson Cancer Center Investigational New Drug Office will have regular contacts with the investigator and team.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor and Genentech Inc with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

The Investigator is responsible for completing the cohort summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 5

evaluable patients, and every 5 evaluable patients, thereafter.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and Genentech Inc and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 ADMINISTRATIVE STRUCTURE

This trial will be supported via the rare disease strategic alliance between The University of Texas MD Anderson Cancer Center and Genentech. The University of Texas MD Anderson Cancer Center will be the sole site, responsible for enrolling approximately 160 total patients.

The MD Anderson Cancer Center IND office will provide oversight of safety (see Section 5.2).

After written informed consent has been obtained, the study team will generate a unique study identification number for the patient.

Patient data will be recorded via an EDC system with use of eCRFs.

Central laboratories, including those at Genentech/Roche/Roche collaborators and at The University of Texas MD Anderson Cancer Center, will be used for PD-L1 expression status determination and will provide kits for pharmacogenomic, tissue, whole blood, serum, and plasma sample analyses to be conducted at central laboratories or Genentech.

Treatment decisions will be made on the basis of the local reading of ECGs obtained during the study.

Imaging data will be retained at The University of Texas MD Anderson Cancer Center.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor and Genentech Inc is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application

has been filed or approved in any country, the PI aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to Genentech Inc prior to submission for publication or presentation. This allows Genentech Inc to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Genentech Inc will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Genentech Inc personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Genentech Inc personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Genentech Inc, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in contact information).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol 2012;30:507–12.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634–46.

DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277–80.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. 2012 Dec. EMA/CHPM/205/95/Rev.4.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Fozza C, Corda G, Virdis P, et al. Derangement of the T-cell repertoire in patients with B-cell non–Hodgkin's lymphoma. Eur J Haematol 2014:1–12.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. J Clin Oncol 2006;24:5545–51.

[FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007 May.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression-free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. BMJ Open 2013;3:1–6.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;12:528–38.

Postow M, Manuel M, Wong P, et al. T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma. J Immunother Cancer 2014;2(Suppl 3):08.

Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a atezolizumab study. J Clin Oncol 2013;31:abstract 3001.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12):2367–75.

Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006;355:2542–50.

Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 2010;11:861–70.

Stinchcombe TE, Socinski MA, Lee CB, et al. Considerations for second-line therapy of non-small cell lung cancer. Oncologist 2008;13:128–36.

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. New Engl J Med 2010;363:733–42.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Appendix 1
Schedule of Activities

	Screening [a]	Odd Treatment Cycles (21-day cycles)	Cycle 1 only	Even Treatment Cycles (21-day cycles)	Cycle 2 only	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±3 days)	Day 8 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	≤30 Days after Last Dose	
Informed consent	x [c]						
Demographic data	x						
Medical history and baseline conditions	x						
Vital signs [e]	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	
Height	x						
Complete physical examination [f]	x					x	
Limited physical examination [g]		x	x	x	x		
ECOG Performance Status	x	x	x	x	x	x	
ECG [h]	x						
Hematology [i]	x [j]	x [k]	x	x	x	x	
Chemistry [l]	x [j]	x [k]	x	x	x	x	

Appendix 1
Schedule of Activities (cont.)

	Screening [a]	Odd Treatment Cycles (21-day cycles)	Cycle 1 only	Even Treatment Cycles (21-day cycles)	Cycle 2 only	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±3 days)	Day 8 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	≤30 Days after Last Dose	
Pregnancy test [m]	x [j]						
Coagulation (INR, aPTT)	x [j]					x	
TSH, free T3 (or total T3 [n]), free T4	x [j]	x [n]				x	
Viral serology [o]	x [j]						
Urinalysis [p]	x [j]	x [q]					
Echo/MUGA	x [r]	x [r]		x [r]			
Blood sample for biomarkers	x [s]			x [s]		x [s]	x [s]
Blood sample for WGS		x					
Tumor biopsy (if clinically feasible)	x			X [t]		X [u]	
Tumor response assessments	x [v]	x [w,x]		x [w,x]			
Concomitant medications [y]	x [y]	x	x	x	x	x	
Adverse events [z]	x [z]	x [z]	x [z]	x [z]	x [z]	x	x [z]
Study treatment administration [aa]		x		x			
Survival follow-up and anti-cancer treatment							x [bb]

Appendix 1
Schedule of Activities (cont.)

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 30 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] A pretreatment tumor biopsy is required.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline on the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.

[m] All women of childbearing potential will have a serum pregnancy test at screening.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter.

Appendix 1
Schedule of Activities (cont.)

[o] At screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[q] Urinalysis should be performed every 6 weeks (2 cycles) during study treatment.

[r] Echo or MUGA to be considered at baseline and thereafter per clinical suspicion

[s] See Appendix 2 for detailed schedule.

[t] On-treatment biopsy will be obtained on Cycle 2 Day 1, +/- 7 days

[u] Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.

[v] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[w] Patients will undergo tumor assessments at baseline and every 9-12 weeks thereafter (with neuroendocrine cohorts 5 and 6 assessed every 12 weeks and all other cohorts assessed every 9 weeks), regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for atezolizumab-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study

treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor and Genentech Inc should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[aa] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day −28 to Day –1)	NA	Biomarker (blood, plasma, and serum)
Day 1 of Cycle 2	Prior to infusion	Biomarker (blood, plasma, and serum)
Progression (≤ 40 days after progression is radiographically determined[j])	NA	Biomarker (blood, plasma, and serum)

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥ 10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point

forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and

qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to $<$10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of $<$10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present

and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR

- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those

gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥30% decrease in tumor burden, [a] in the absence of CR
PD	≥20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 mm but $<$15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and $\geq$10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

<u>ASSESSMENT OF TUMOR BURDEN</u>

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative

of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non–lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is $<$10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is $\geq$15 mm.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to $<$15 mm (or even $<$10 mm). However, if it subsequently decreases to $<$10 mm and all other lesions are no longer detectable or have also decreased to a short axis of $<$10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to $<$10 mm during the study. Thus, when lymph nodes are included in the

sum of diameters, the sum may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

Definitions of the criteria used to determine objective tumor response are provided below:

- Complete response (CR): Disappearance of all lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

  New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target or measurable new lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 1.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Can 2014;2:17

Appendix 5
Preexisting Autoimmune Diseases and Immune Deficiencies

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 6
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations

Appendix 7
Additional References

ALAKUS, H., BABICKY, M. L., GHOSH, P., YOST, S., JEPSEN, K., DAI, Y., ARIAS, A., SAMUELS, M. L., MOSE, E. S., SCHWAB, R. B., PETERSON, M. R., LOWY, A. M., FRAZER, K. A. & HARISMENDY, O. 2014. Genome-wide mutational landscape of mucinous carcinomatosis peritonei of appendiceal origin. *Genome Med,* 6**,** 43.

ASARE, E. A., COMPTON, C. C., HANNA, N. N., KOSINSKI, L. A., WASHINGTON, M. K., KAKAR, S., WEISER, M. R. & OVERMAN, M. J. 2016. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: Analysis of the National Cancer Data Base. *Cancer,* 122**,** 213-21.

BARBER, D. L., WHERRY, E. J., MASOPUST, D., ZHU, B., ALLISON, J. P., SHARPE, A. H., FREEMAN, G. J. & AHMED, R. 2006. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature,* 439**,** 682-7.

BENNOUNA, J., SASTRE, J., ARNOLD, D., OSTERLUND, P., GREIL, R., VAN CUTSEM, E., VON MOOS, R., VIEITEZ, J. M., BOUCHE, O., BORG, C., STEFFENS, C. C., ALONSO-ORDUNA, V., SCHLICHTING, C., REYES-RIVERA, I., BENDAHMANE, B., ANDRE, T., KUBICKA, S. & INVESTIGATORS, M. L. S. 2013. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol,* 14**,** 29-37.

BHATIA, S., AFANASIEV, O. & NGHIEM, P. 2011. Immunobiology of Merkel cell carcinoma: implications for immunotherapy of a polyomavirus-associated cancer. *Curr Oncol Rep,* 13**,** 488-97.

BLANK, C., GAJEWSKI, T. F. & MACKENSEN, A. 2005. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol Immunother,* 54**,** 307-14.

BRAHMER, J., RIZVI, N., LUTZKY, J., KHLEIF, S., BLAKE-HASKINS, A., LI, X., ROBBINS, P., VASSELLI, J., IBRAHIM, R. & ANTONIA, S. 2014. Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. *Journal of Clinical Oncology* 32**,** Abstract 8021

BRAHMER, J. R. 2013. Harnessing the immune system for the treatment of non-small-cell lung cancer. *J Clin Oncol,* 31**,** 1021-8.

BRAHMER, J. R., TYKODI, S. S., CHOW, L. Q., HWU, W. J., TOPALIAN, S. L., HWU, P., DRAKE, C. G., CAMACHO, L. H., KAUH, J., ODUNSI, K., PITOT, H. C., HAMID, O., BHATIA, S., MARTINS, R., EATON, K., CHEN, S., SALAY, T. M., ALAPARTHY, S., GROSSO, J. F., KORMAN, A. J., PARKER, S. M., AGRAWAL, S., GOLDBERG, S. M., PARDOLL, D. M., GUPTA, A. & WIGGINTON, J. M. 2012. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med,* 366**,** 2455-65.

BRUNNER, M., THURNHER, D., PAMMER, J., GELEFF, S., HEIDUSCHKA, G., REINISCH, C. M., PETZELBAUER, P. & EROVIC, B. M. 2008. Expression of VEGF-A/C, VEGF-R2, PDGF-alpha/beta, c-kit, EGFR, Her-2/Neu, Mcl-1 and Bmi-1 in Merkel cell carcinoma. *Mod Pathol,* 21**,** 876-84.

CALABRO, L., MORRA, A., FONSATTI, E., CUTAIA, O., AMATO, G., GIANNARELLI, D., DI GIACOMO, A. M., DANIELLI, R., ALTOMONTE, M., MUTTI, L. & MAIO, M.

Appendix 7
Additional References (cont.)

2013. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *Lancet Oncol,* 14**,** 1104-11.

CAPLIN, M. E., PAVEL, M., CWIKLA, J. B., PHAN, A. T., RADERER, M., SEDLACKOVA, E., CADIOT, G., WOLIN, E. M., CAPDEVILA, J., WALL, L., RINDI, G., LANGLEY, A., MARTINEZ, S., BLUMBERG, J., RUSZNIEWSKI, P. & INVESTIGATORS, C. 2014. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med,* 371**,** 224-33.

CARR, N. J., CECIL, T. D., MOHAMED, F., SOBIN, L. H., SUGARBAKER, P. H., GONZALEZ-MORENO, S., TAFLAMPAS, P., CHAPMAN, S. & MORAN, B. J. 2016. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol,* 40**,** 14-26.

CHEN, D. S., IRVING, B. A. & HODI, F. S. 2012. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res,* 18**,** 6580-7.

CHO, C. S., LABOW, D. M., TANG, L., KLIMSTRA, D. S., LOEFFLER, A. G., LEVERSON, G. E., FONG, Y., JARNAGIN, W. R., D'ANGELICA, M. I., WEBER, S. M., BLUMGART, L. H. & DEMATTEO, R. P. 2008. Histologic grade is correlated with outcome after resection of hepatic neuroendocrine neoplasms. *Cancer,* 113**,** 126-34.

CHUA, D. T., SHAM, J. S. & AU, G. K. 2003. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol,* 39**,** 361-6.

DAVIES, M. 2014. New modalities of cancer treatment for NSCLC: focus on immunotherapy. *Cancer Manag Res,* 6**,** 63-75.

DAY, C. L., KAUFMANN, D. E., KIEPIELA, P., BROWN, J. A., MOODLEY, E. S., REDDY, S., MACKEY, E. W., MILLER, J. D., LESLIE, A. J., DEPIERRES, C., MNCUBE, Z., DURAISWAMY, J., ZHU, B., EICHBAUM, Q., ALTFELD, M., WHERRY, E. J., COOVADIA, H. M., GOULDER, P. J., KLENERMAN, P., AHMED, R., FREEMAN, G. J. & WALKER, B. D. 2006. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature,* 443**,** 350-4.

FANG, W., ZHANG, J., HONG, S., ZHAN, J., CHEN, N., QIN, T., TANG, Y., ZHANG, Y., KANG, S., ZHOU, T., WU, X., LIANG, W., HU, Z., MA, Y., ZHAO, Y., TIAN, Y., YANG, Y., XUE, C., YAN, Y., HOU, X., HUANG, P., HUANG, Y., ZHAO, H. & ZHANG, L. 2014. EBV-driven LMP1 and IFN-gamma up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. *Oncotarget,* 5**,** 12189-202.

FEHRENBACHER, L., SPIRA, A., BALLINGER, M., KOWANETZ, M., VANSTEENKISTE, J., MAZIERES, J., PARK, K., SMITH, D., ARTAL-CORTES, A., LEWANSKI, C., BRAITEH, F., WATERKAMP, D., HE, P., ZOU, W., CHEN, D. S., YI, J., SANDLER, A., RITTMEYER, A. & GROUP, P. S. 2016. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet,* 387**,** 1837-46.

Appendix 7
Additional References (cont.)

FENG, H., SHUDA, M., CHANG, Y. & MOORE, P. S. 2008. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science,* 319**,** 1096-100.

FOO, K. F., TAN, E. H., LEONG, S. S., WEE, J. T., TAN, T., FONG, K. W., KOH, L., TAI, B. C., LIAN, L. G. & MACHIN, D. 2002. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol,* 13**,** 150-6.

FORMAN, D., DE MARTEL, C., LACEY, C. J., SOERJOMATARAM, I., LORTET-TIEULENT, J., BRUNI, L., VIGNAT, J., FERLAY, J., BRAY, F., PLUMMER, M. & FRANCESCHI, S. 2012. Global burden of human papillomavirus and related diseases. *Vaccine,* 30 Suppl 5**,** F12-23.

HODI, F. S., LAWRENCE, D., LEZCANO, C., WU, X., ZHOU, J., SASADA, T., ZENG, W., GIOBBIE-HURDER, A., ATKINS, M. B., IBRAHIM, N., FRIEDLANDER, P., FLAHERTY, K. T., MURPHY, G. F., RODIG, S., VELAZQUEZ, E. F., MIHM, M. C., JR., RUSSELL, S., DIPIRO, P. J., YAP, J. T., RAMAIYA, N., VAN DEN ABBEELE, A. D., GARGANO, M. & MCDERMOTT, D. 2014. Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res,* 2**,** 632-42.

HODI, F. S., O'DAY, S. J., MCDERMOTT, D. F., WEBER, R. W., SOSMAN, J. A., HAANEN, J. B., GONZALEZ, R., ROBERT, C., SCHADENDORF, D., HASSEL, J. C., AKERLEY, W., VAN DEN EERTWEGH, A. J., LUTZKY, J., LORIGAN, P., VAUBEL, J. M., LINETTE, G. P., HOGG, D., OTTENSMEIER, C. H., LEBBE, C., PESCHEL, C., QUIRT, I., CLARK, J. I., WOLCHOK, J. D., WEBER, J. S., TIAN, J., YELLIN, M. J., NICHOL, G. M., HOOS, A. & URBA, W. J. 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med,* 363**,** 711-23.

JANNE, P. A., WOZNIAK, A. J., BELANI, C. P., KEOHAN, M. L., ROSS, H. J., POLIKOFF, J. A., MINTZER, D. M., TAYLOR, L., ASHLAND, J., YE, Z., MONBERG, M. J. & OBASAJU, C. K. 2005. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer,* 7**,** 40-6.

KANTOFF, P. W., HIGANO, C. S., SHORE, N. D., BERGER, E. R., SMALL, E. J., PENSON, D. F., REDFERN, C. H., FERRARI, A. C., DREICER, R., SIMS, R. B., XU, Y., FROHLICH, M. W., SCHELLHAMMER, P. F. & INVESTIGATORS, I. S. 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med,* 363**,** 411-22.

KARIM, S. & LEIGHL, N. 2016. Pembrolizumab for the treatment of thoracic malignancies: current landscape and future directions. *Future Oncol,* 12**,** 9-23.

KEIR, M. E., BUTTE, M. J., FREEMAN, G. J. & SHARPE, A. H. 2008. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol,* 26**,** 677-704.

KOUVARAKI, M. A., AJANI, J. A., HOFF, P., WOLFF, R., EVANS, D. B., LOZANO, R. & YAO, J. C. 2004. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 22**,** 4762-71.

KRISHNA, S. M., JAMES, S. & BALARAM, P. 2006. Expression of VEGF as prognosticator in primary nasopharyngeal cancer and its relation to EBV status. *Virus Res,* 115**,** 85-90.

Appendix 7
Additional References (cont.)

KUKKO, H., KOLJONEN, V., LASSUS, P., TUKIAINEN, E., HAGLUND, C. & BOHLING, T. 2007. Expression of vascular endothelial growth factor receptor-2 in Merkel cell carcinoma. *Anticancer Res,* 27**,** 2587-9.

LEE, N. Y., ZHANG, Q., PFISTER, D. G., KIM, J., GARDEN, A. S., MECHALAKOS, J., HU, K., LE, Q. T., COLEVAS, A. D., GLISSON, B. S., CHAN, A. T. & ANG, K. K. 2012. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. *Lancet Oncol,* 13**,** 172-80.

LEMOS, B. D., STORER, B. E., IYER, J. G., PHILLIPS, J. L., BICHAKJIAN, C. K., FANG, L. C., JOHNSON, T. M., LIEGEOIS-KWON, N. J., OTLEY, C. C., PAULSON, K. G., ROSS, M. I., YU, S. S., ZEITOUNI, N. C., BYRD, D. R., SONDAK, V. K., GERSHENWALD, J. E., SOBER, A. J. & NGHIEM, P. 2010. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol,* 63**,** 751-61.

LIPSON, E. J., VINCENT, J. G., LOYO, M., KAGOHARA, L. T., LUBER, B. S., WANG, H., XU, H., NAYAR, S. K., WANG, T. S., SIDRANSKY, D., ANDERS, R. A., TOPALIAN, S. L. & TAUBE, J. M. 2013. PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. *Cancer Immunol Res,* 1**,** 54-63.

MANSFIELD, A., PEIKERT, T., RODEN, A., KRCO, C., HARRINGTON, S., DONG, H. & KWON, E. 2014. Programmed cell death 1 ligand 1 expression and association with survival in mesothelioma. *Journal of Thoracic Oncology,* 9 S7-S52.

MANZONI, M., ROVATI, B., RONZONI, M., LOUPAKIS, F., MARIUCCI, S., RICCI, V., GATTONI, E., SALVATORE, L., TINELLI, C., VILLA, E. & DANOVA, M. 2010. Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer. *Oncology,* 79**,** 187-96.

MCCUSKER, M. E., COTE, T. R., CLEGG, L. X. & SOBIN, L. H. 2002. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer,* 94**,** 3307-12.

MOERTEL, C. G., HANLEY, J. A. & JOHNSON, L. A. 1980. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *The New England journal of medicine,* 303**,** 1189-94.

MOERTEL, C. G., LEFKOPOULO, M., LIPSITZ, S., HAHN, R. G. & KLAASSEN, D. 1992. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *The New England journal of medicine,* 326**,** 519-23.

NGEOW, J., LIM, W. T., LEONG, S. S., ANG, M. K., TOH, C. K., GAO, F., CHOWBAY, B. & TAN, E. H. 2011. Docetaxel is effective in heavily pretreated patients with disseminated nasopharyngeal carcinoma. *Ann Oncol,* 22**,** 718-22.

NGHIEM, P. T., BHATIA, S., LIPSON, E. J., KUDCHADKAR, R. R., MILLER, N. J., ANNAMALAI, L., BERRY, S., CHARTASH, E. K., DAUD, A., FLING, S. P., FRIEDLANDER, P. A., KLUGER, H. M., KOHRT, H. E., LUNDGREN, L., MARGOLIN, K., MITCHELL, A., OLENCKI, T., PARDOLL, D. M., REDDY, S. A., SHANTHA, E. M., SHARFMAN, W. H., SHARON, E., SHEMANSKI, L. R., SHINOHARA, M. M., SUNSHINE, J. C., TAUBE, J. M., THOMPSON, J. A., TOWNSON, S. M., YEARLEY, J. H., TOPALIAN, S. L. & CHEEVER, M. A. 2016.

Appendix 7
Additional References (cont.)

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med,* 374**,** 2542-52.

OXNARD, G. R., WILCOX, K. H., GONEN, M., POLOTSKY, M., HIRSCH, B. R. & SCHWARTZ, L. H. 2016. Response Rate as a Regulatory End Point in Single-Arm Studies of Advanced Solid Tumors. *JAMA Oncol,* 2**,** 772-9.

QIAN, C. N., ZHANG, C. Q., GUO, X., HONG, M. H., CAO, S. M., MAI, W. Y., MIN, H. Q. & ZENG, Y. X. 2000. Elevation of serum vascular endothelial growth factor in male patients with metastatic nasopharyngeal carcinoma. *Cancer,* 88**,** 255-61.

RAGHAV, K. P., SHETTY, A. V., KAZMI, S. M., ZHANG, N., MORRIS, J., TAGGART, M., FOURNIER, K., ROYAL, R., MANSFIELD, P., ENG, C., WOLFF, R. A. & OVERMAN, M. J. 2013. Impact of molecular alterations and targeted therapy in appendiceal adenocarcinomas. *Oncologist,* 18**,** 1270-7.

RAYMOND, E., DAHAN, L., RAOUL, J.-L., BANG, Y.-J., BORBATH, I., LOMBARD-BOHAS, C., VALLE, J., METRAKOS, P., SMITH, D., VINIK, A., CHEN, J.-S., HÖRSCH, D., HAMMEL, P., WIEDENMANN, B., VAN CUTSEM, E., PATYNA, S., LU, D. R., BLANCKMEISTER, C., CHAO, R. & RUSZNIEWSKI, P. 2011. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *The New England journal of medicine,* 364**,** 501-13.

RINKE, A., MULLER, H. H., SCHADE-BRITTINGER, C., KLOSE, K. J., BARTH, P., WIED, M., MAYER, C., AMINOSSADATI, B., PAPE, U. F., BLAKER, M., HARDER, J., ARNOLD, C., GRESS, T., ARNOLD, R. & GROUP, P. S. 2009. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol,* 27**,** 4656-63.

RODRIGUEZ, D., CHEUNG, M. C., HOUSRI, N. & KONIARIS, L. G. 2009. Malignant abdominal mesothelioma: defining the role of surgery. *J Surg Oncol,* 99**,** 51-7.

ROLLISON, D. E., GIULIANO, A. R. & BECKER, J. C. 2010. New virus associated with merkel cell carcinoma development. *J Natl Compr Canc Netw,* 8**,** 874-80.

ROSENBERG, J. E., HOFFMAN-CENSITS, J., POWLES, T., VAN DER HEIJDEN, M. S., BALAR, A. V., NECCHI, A., DAWSON, N., O'DONNELL, P. H., BALMANOUKIAN, A., LORIOT, Y., SRINIVAS, S., RETZ, M. M., GRIVAS, P., JOSEPH, R. W., GALSKY, M. D., FLEMING, M. T., PETRYLAK, D. P., PEREZ-GRACIA, J. L., BURRIS, H. A., CASTELLANO, D., CANIL, C., BELLMUNT, J., BAJORIN, D., NICKLES, D., BOURGON, R., FRAMPTON, G. M., CUI, N., MARIATHASAN, S., ABIDOYE, O., FINE, G. D. & DREICER, R. 2016. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet,* 387**,** 1909-20.

SMEENK, R. M., VERWAAL, V. J., ANTONINI, N. & ZOETMULDER, F. A. 2007. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg,* 245**,** 104-9.

STEBBING, J., POWLES, T., MCPHERSON, K., SHAMASH, J., WELLS, P., SHEAFF, M. T., SLATER, S., RUDD, R. M., FENNELL, D. & STEELE, J. P. 2009. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer,* 63**,** 94-7.

THOMAS, A. & HASSAN, R. 2012. Immunotherapies for non-small-cell lung cancer and mesothelioma. *Lancet Oncol,* 13**,** e301-10.

Appendix 7
Additional References (cont.)

TSAO, A. S., WISTUBA, I., ROTH, J. A. & KINDLER, H. L. 2009. Malignant pleural mesothelioma. *J Clin Oncol,* 27**,** 2081-90.

VAN MEERBEECK, J. P., BAAS, P., DEBRUYNE, C., GROEN, H. J., MANEGOLD, C., ARDIZZONI, A., GRIDELLI, C., VAN MARCK, E. A., LENTZ, M. & GIACCONE, G. 1999. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer,* 85**,** 2577-82.

VOGELZANG, N. J., RUSTHOVEN, J. J., SYMANOWSKI, J., DENHAM, C., KAUKEL, E., RUFFIE, P., GATZEMEIER, U., BOYER, M., EMRI, S., MANEGOLD, C., NIYIKIZA, C. & PAOLETTI, P. 2003. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol,* 21**,** 2636-44.

YAO, J. C., HASSAN, M., PHAN, A., DAGOHOY, C., LEARY, C., MARES, J. E., ABDALLA, E. K., FLEMING, J. B., VAUTHEY, J.-N., RASHID, A. & EVANS, D. B. 2008. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 26**,** 3063-72.

YAO, J. C., LOMBARD-BOHAS, C., BAUDIN, E., KVOLS, L. K., ROUGIER, P., RUSZNIEWSKI, P., HOOSEN, S., ST PETER, J., HAAS, T., LEBWOHL, D., VAN CUTSEM, E., KULKE, M. H., HOBDAY, T. J., O'DORISIO, T. M., SHAH, M. H., CADIOT, G., LUPPI, G., POSEY, J. A. & WIEDENMANN, B. 2010. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 28**,** 69-76.

ZALCMAN, G., MAZIERES, J., MARGERY, J., GREILLIER, L., AUDIGIER-VALETTE, C., MORO-SIBILOT, D., MOLINIER, O., CORRE, R., MONNET, I., GOUNANT, V., RIVIERE, F., JANICOT, H., GERVAIS, R., LOCHER, C., MILLERON, B., TRAN, Q., LEBITASY, M. P., MORIN, F., CREVEUIL, C., PARIENTI, J. J., SCHERPEREEL, A. & FRENCH COOPERATIVE THORACIC, I. 2015. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*.

ZALCMAN, G., MAZIERES, J., MARGERY, J., GREILLIER, L., AUDIGIER-VALETTE, C., MORO-SIBILOT, D., MOLINIER, O., CORRE, R., MONNET, I., GOUNANT, V., RIVIERE, F., JANICOT, H., GERVAIS, R., LOCHER, C., MILLERON, B., TRAN, Q., LEBITASY, M. P., MORIN, F., CREVEUIL, C., PARIENTI, J. J., SCHERPEREEL, A. & FRENCH COOPERATIVE THORACIC, I. 2016. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet,* 387**,** 1405-14.

Document comparison between final and original documents

PROTOCOL

TITLE:	**A PHASE II, SINGLE-ARM OPEN-LABEL STUDY OF THE COMBINATION OF ATEZOLIZUMAB AND BEVACIZUMAB IN RARE SOLID TUMORS**
MD ANDERSON CANCER CENTER PROTOCOL NUMBER	2016-0861
GENENTECH PROTOCOL NUMBER:	ML39572
VERSION NUMBER:	12
VERSION DATE	3/11/2019
EUDRACT NUMBER:	Not Applicable
IND NUMBER:	133805
INVESTIGATOR	Daniel M. Halperin, MD 1515 Holcombe Blvd Unit 426 Houston, TX 77030 Telephone: 713-792-2828 Fax: 713-745-1163 E-mail: dmhalperin@mdanderson.org
TEST PRODUCTS:	Atezolizumab (RO5541267) Bevacizumab
MEDICAL MONITOR:	UT M.D. Anderson IND Office
SPONSOR:	UT M.D. Anderson
DATE FINAL:	See electronic date stamp below

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DMC	Data Monitoring Committee
EBV	Epstein-Barr Virus
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
LPLV	last patient, last visit
MTD	maximum tolerated dose
NCI	National Cancer Institute
NET	Neuroendocrine Tumor
ORR	objective response rate
PI	Principal investigator
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q3W	every 3 weeks
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
TC	tumor cell
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON THE SPECIFIC SOLID TUMORS BEING STUDIED

1.1.1 Appendiceal adenocarcinoma

Appendiceal tumors are rare, with an age-adjusted incidence of 0.12 cases per 1,000,000 per year.(McCusker et al., 2002) Metastatic appendiceal neoplasms are tumors characterized by a relatively indolent natural clinical course if low-grade and very aggressive biology if high grade.(Asare et al., 2016, Carr et al., 2016) Cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard therapy in low-grade tumors and results in prolonged survival, but is not effective in high grade tumors, where systemic therapy is the only option, but has limited benefit.(Smeenk et al., 2007) However, high tumor burden and medical comorbidities can exclude patients from curative intent surgery. Conventional cytotoxic chemotherapy in these patients has shown no or little clinical benefit.(Asare et al., 2016) There exists an unmet need for active targeted agents in this setting. Emerging data has shown a higher frequency of KRAS mutations in low-grade appendiceal neoplasms (70%-80%) compared to high-grade tumors.(Raghav et al., 2013, Alakus et al., 2014) Appendiceal adenocarcinomas mimic colorectal cancer to a large extent and are treated similarly. Immunotherapy has only been effective in microsatellite-unstable colorectal cancer, and novel strategies of immunomodulation are therefore needed in the treatment of cancers of the lower gastrointestinal tract.

1.1.2 Nasopharyngeal carcinoma

Approximately 3,200 cases of nasopharyngeal carcinoma (NPC) are diagnosed yearly in the USA. Unfortunately, there are no standard of care systemic treatments for patients with recurrent or metastatic NPC. Platinum-based chemotherapy is frequently used in the first line setting. In the second line and beyond, monotherapy regimens with gemcitabine, capecitabine, or docetaxel(Chua et al., 2003, Foo et al., 2002, Ngeow et al., 2011) are frequently used, with responses rates of approximately 30% and a median PFS of only 5 months.

NPC is an Epstein Barr Virus (EBV) driven malignancy. Chronic EBV infection leads to increased viral EBV load and expression of PD-1 on cytotoxic memory T-cells leading to T-cell exhaustion (Barber et al., 2006, Day et al., 2006). Increased PD-1 expression also occurs in the virally affected host cells. Latent EBV infection is also associated with expression of LMP-1 protein which induces PD-L1 expression (Fang et al., 2014). Increased PD-1 and PD-L1 work together to suppress the immune system, leading to decreased EBV cellular immunity. PD-L1 expression is almost universal in NPC (98% of cases) and clinical activity of PD-1 inhibitor single agent has been reported in a cohort of patients with refractory NPC [Hsu, ESMO 2015].

VEGF concentrations are substantially increased in patients with metastatic NPC(Qian et al., 2000). The higher expression of VEGF in EBV related tumors is related to higher rates of recurrence and shorter overall survival(Krishna et al., 2006). Bevacizumab given with

concurrent chemoradiation has been studied in NPC with promising results (Lee et al., 2012). VEGF suppresses the immune system and the combination of bevacizumab with checkpoint inhibitor has rendered encouraging results in metastatic melanoma (Hodi et al., 2014). Taken together, there is a strong rationale to study the anti-PD-L1/anti-VEGF combination in metastatic NPC, a highly unmet clinical need.

1.1.3 Human Papilloma Virus (HPV)-associated cancers

The human papilloma virus (HPV) is associated with the development of multiple malignancies including cervical, oropharyngeal, vulvar, vagina, penile, and anal cancer. In 2008, of the estimated 12.7 million cancers, 610,000 cases are believed to be attributed to HPV (Forman et al., 2012). It is estimated 89,000 patients will be diagnosed worldwide with the rare HPV associated cancers: vulvar, vagina, penile, and anal cancer [Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Muñoz J, Bosch FX, de Sanjosé S, Castellsagué X. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 2016- 02-25. [7/15/16]. The association of HPV has been well documented in both cervical and oropharyngeal cancer, as well. Each of these cancers has been linked to HPV in variable degrees: 90% of anal, cervical, and vaginal carcinomas; 70% of all vulvar cancers; and 50% of penile cancers. Currently, there is no standard treatment approach for patients with metastatic disease for these rare cancers, nor is there a standard of care for cervical cancer refractory to platinum-based chemotherapy. In short, clinical trial development has been lacking for these malignancies. Yet, there is a rising incidence of HPV associated cancers, notably anal and oropharyngeal cancers (www.seer.gov). Identification of treatment options for the HPV associated malignancies of metastatic or surgically unresectable anal, penile, and vaginal, vulvar, and refractory cervical cancer, is clearly an unmet need. Intriguingly, treatment with the immune checkpoint inhibitor, nivolumab, in refractory metastatic squamous cell carcinoma of the anal canal (NCI9673) yielded initial proof of concept of the activity of immunotherapy against an HPV-associated malignancy, with an overall response rate of 24% (CR rate of 5%; PR rate of 19%) [Morris et al., ASCO 2016].

1.1.4 Merkel Cell Carcinoma

Merkel Cell Carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, with an estimate incidence of 1,500 new cases per year in the US, which is rising. Patients with metastatic disease have a 2-year survival of approximately 25%, representing a major unmet clinical need (Lemos et al., 2010). Currently, there is no FDA approved treatment for unresectable, recurrent, or metastatic MCC. Given it is a high-grade neuroendocrine carcinoma, patients are usually treated with chemotherapy regimens frequently used in small cell lung cancer [NCCN guidelines], however, responses are of short duration and the benefit of chemotherapy is questionable. MCC is associated with the Merkel cell polyomavirus in 40-100% of the cases (Feng et al., 2008, Rollison et al., 2010). The risk of developing MCC is increased from 5 to 50-fold in immunocompromised individuals, and there are reports of tumor regression following improvement in immune system

function(Bhatia et al., 2011). PD-L1 expression is seen in 49% of MCC and expression in tumor-infiltrating lymphocytes occurs in 55% of the patients (Lipson et al., 2013). Recently, encouraging activity has been reported with single agent anti-PD1 in this patient population (Nghiem et al., 2016). VEGF-A, VEGF-C and VEGFR2 overexpression is also prevalent in MCC and correlates with metastatic potential (Brunner et al., 2008, Kukko et al., 2007). Thus, there is significant rationale for pursuing dual VEGF and PD-L1 blockade.

1.1.5 Neuroendocrine tumors, pancreatic and extra pancreatic

Well-differentiated neuroendocrine tumors (NETs) are relatively rare malignancies of a diffuse neuroendocrine network with a variable clinical course, and median survival ranging from 24 months to over ten years(Yao et al., 2008). Because of differences in effective therapy, they are often classified as either pancreatic NETs (pNETs) or extra pancreatic NETs. The mTOR inhibitor everolimus and the somatostatin analogues lanreotide and octreotide are the only drugs approved for the oncologic management of gastrointestinal NETs (Caplin et al., 2014, Rinke et al., 2009). In contrast, chemotherapy is standard in pancreatic NETs (PNETs) (Moertel et al., 1980, Moertel et al., 1992, Kouvaraki et al., 2004), as is the somatostatin analogue lanreotide (Caplin et al., 2014) and targeted agents such as everolimus(Yao et al., 2010) and sunitinib (Raymond et al., 2011). pNETs remain life-limiting, and response rates are universally less than 10%. Additional therapies are therefore desperately lacking for NETs. Immunotherapy, such as with interferon, as well as anti-VEGF therapy with bevacizumab and sunitinib, have been investigational and standard therapies in the NET field for decades, but the two strategies have never been tested in combination.

1.1.6 Peritoneal mesothelioma

Malignant peritoneal mesothelioma (MPM) is a rare disease and constitutes about 10% of all cases of malignant mesothelioma.(Rodriguez et al., 2009) With an annual incidence of 1 per 100,000 population, approximately 300 – 400 cases are diagnosed in the United States every year.(Rodriguez et al., 2009) Current options for systemic therapy are limited and afford modest survival benefit.(Janne et al., 2005, Vogelzang et al., 2003) The standard of care for frontline unresectable MPM is platinum-pemetrexed.(Vogelzang et al., 2003, Janne et al., 2005) Beyond the first-line therapy, no good standard of care or FDA approved agents exist. Single agent gemcitabine and vinorelbine are used in the salvage setting due to modest activity seen in pleural mesothelioma (response rate 8-16%) and are riddled with toxicity.(van Meerbeeck et al., 1999, Stebbing et al., 2009) Historically, the progression-free survival (PFS) in this setting is about 1.7 months (Stebbing et al., 2009, van Meerbeeck et al., 1999) Therefore, there is an unmet and critical need to develop novel agents for this orphan disease. Tremelimumab, a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA4), has shown encouraging clinical activity and acceptable safety profile in refractory patients with malignant pleural mesothelioma with a disease control rate of 30% and a PFS of 6.2 months.(Calabro et al., 2013) The preliminary results of KEYNOTE-028 trial with a cohort of patients (N = 25) with malignant pleural mesothelioma (AACR 2015) showed an ORR of 28% and SD in 48% patients.(Karim and

Leighl, 2016) One of our patients with MPM treated with Atezo on protocol 2015-0239, who was refractory to cisplatin and pemetrexed received a major response at first restaging. Addition of bevacizumab to chemotherapy significantly improves OS in malignant mesothelioma and is currently being considered for regulatory approval (Zalcman et al., 2016). Furthermore, VEGF leads to a functional defect of the dendritic cells and decreased antigen presentation and inhibition with bevacizumab increases B and T cell compartments (Manzoni et al., 2010). Therefore combining two potentially active therapies with plausible synergistic effects could help antitumor efficacy of this combination in mesothelioma.

1.1.7 Pleural mesothelioma

Malignant mesothelioma (MM) is an orphan disease that is difficult to treat.(Tsao et al., 2009) Novel agents are critically needed as the median overall survival with advanced MM is 1 year and there are no FDA approved agents in the salvage setting. In the past year, The Intergroupe Francophone de Cancerologie Thoracique (IFCT) published their positive results on the Phase III MAPS trial which compared cisplatin-pemetrexed with and without bevacizumab. Both the PFS (HR 0.61, p<0.0001) and OS (HR 0.77, p=0.0167) were prolonged in the patients who received bevacizumab (Zalcman et al., 2015). This is the first triplet regimen with a novel biologic agent that has demonstrated a clear survival benefit to MM patients, and is undergoing evaluation for regulatory approval.

Programmed death 1 (PD1) protein, a T-cell co-inhibitory receptor, and one of its ligands PD-L1 are targets for immunotherapy. PD-1 receptor binds with PD-L1 and inhibits T-cell inhibition and downregulates T-cell responses. Inhibition of their interaction has been shown to lead to restoration of T-cell activity and a subsequent anti-tumor effect in several tumor types. There are several PD-L1 inhibitors under development; to name a few, BMS0936559 (Bristol-Meyers Squibb), MEDI-4736 (Medimmune), and atezolizumab (Genentech) (Brahmer et al., 2012, Brahmer et al., 2014, Davies, 2014). In non-small cell lung cancer, response rates ranging from 10% to 26% have been reported using these PD-L1 inhibitors as monotherapy in Phase I and II trials (Brahmer et al., 2014, Brahmer, 2013, Brahmer et al., 2012, Davies, 2014). MM is anticipated to be a highly immunogenic disease (Thomas and Hassan, 2012). At ESMO 2014, Mansfield et al. (Mansfield et al., 2014) reported a 40% PD-L1 IHC expression in pleural mesotheliomas (n=224) using a mouse monoclonal anti-human B7-H1 (clone 5H1-A3). PD-L1 IHC expression was associated with more disease burden and less offers of surgery to the patient. Also, PD-L1 IHC expression was associated with a worse survival 6 months vs 14 months, p<0.0001) (Mansfield et al., 2014). At AACR 2015, pembrolizumab was shown in 25 mesothelioma patients to have an overall response rate of 28% and 48% stable disease for a disease control rate of 76%. There were no new safety signals with this regimen.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also

known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al., 2016, Rosenberg et al., 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma or non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 BACKGROUND ON BEVACIZUMAB

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 22,000 patients and in multiple tumor types. Approximately 1,720,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab’s safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.66 ($p < 0.001$) and a median survival of 20.3 vs. 15.6 months. Similar increases were seen in progression-free survival (10.6 vs. 6.2 months; HR 0.54, $p < 0.001$), overall response rate (34.8% vs. 44.8%; $p = 0.004$) and duration of response (10.4 vs. 7.1 months; HR 0.62, $p = 0.001$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, November 2012). Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5 FU−based chemotherapy for subjects with metastatic colorectal cancer.

Bevacizumab has also been approved based on additional Phase III trials in metastatic CRC (E3200 and ML18147) non−small cell lung cancer (NSCLC; E4599), and renal cell

carcinoma (RCC; AVOREN) which also demonstrated clinical benefit from bevacizumab. Furthermore, Phase II studies in glioblastoma (GBM; AVF3708g and NCI-06-C0064) showed an improvement in objective response rate. These studies led to accelerated approval by the FDA for recurrent GBM.

In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated, Avastin naive metastatic CRC patients. In Study ML18147, bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy regimens demonstrated a statistically significant increase in OS compared to oxaliplatin- or irinotecan-based chemotherapy alone (11.2 vs. 9.8 months, respectively, HR = 0.81; p=0.0062) in metastatic CRC patients who had previously received bevacizumab as a part of their 1st line treatment (Bennouna et al., 2013). These two studies led to FDA approvals for bevacizumab for previously treated metastatic CRC patients, in 2006 and 2013, respectively.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; p = 0.003). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006.

In previously untreated metastatic RCC patients, bevacizumab in combination with interferon-alfa showed an improved progression free survival compared to interferon-alfa alone (10.2 vs. 5.4 months, respectively; HR=0.63; p=0.0001). These results supported the FDA approval of bevacizumab with interferon-alfa in metastatic RCC in July 2009.

Two Phase II trials investigated bevacizumab as a single agent in patients with recurrent GBM. In AVF3708g, patients with recurrent GBM were randomized to bevacizumab or bevacizumab plus irinotecan and demonstrated an improvement in objective response rate (28.2% vs. 37.8%, respectively). The NCI-06-C0064 study was single arm Phase II study in recurrent GBM patients treated with bevacizumab alone and showed an objective response rate of 19.6%. This study supported the results from AVF3708g, and based on the objective response rate in these two trials, the FDA granted accelerated approval for bevacizumab as a single agent in GBM patients with progressive disease following prior therapy. In 2013, results from two phase III randomized controlled trials for newly diagnosed GBM were presented, one Roche-sponsored trial (AVAglio) and one cooperative group trial (RTOG 0825). In AVAglio, progression free survival was significantly longer with bevacizumab when added to radiation therapy/temozolomide (HR 0.64, mPFS 10.6 vs 6.2 months). Health-related quality of life (HRQoL) and Karnofsky performance score (KPS) were stable/improved during PFS (both arms). Patients receiving bevacizumab plus radiation therapy/temozolomide had diminished corticosteroid requirement, but reported more adverse events (AEs) compared with placebo plus

radiation therapy/temozolomide (serious AEs: 36.6% vs 25.7%; grade ≥3: 62.7% vs 50.1%; grade ≥3 AEs of special interest to bevacizumab: 28.7% vs 15.2%). In RTOG 0825, PFS was extended for bevacizumab (7.3 vs.10.7 months, HR 0.79) but did not meet the pre-specified endpoint for significance. There was no difference between arms for overall survival (median 16.1 vs.15.7 months, HR 1.13).

Lastly, in the E2100 study, patients with untreated metastatic breast cancer who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively, HR 0.48; $p<0.0001$) and this led to the accelerated approval of bevacizumab in metastatic breast cancer. Unfortunately, the clinical benefit was not confirmed in subsequent trials and the FDA ultimately removed the label for the breast cancer indication. (See the Bevacizumab Investigator Brochure for additional details).

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite recent advances in the treatment of more common cancers, patients with rare solid tumors have seen slow progress in recent years. For the reasons specified in Section 1.1, each of the tumor types being investigated in this study has strong preclinical and/or clinical rationale for a study of checkpoint inhibition in combination with VEGF inhibition, and presents an unmet medical need in the metastatic setting. It is therefore imperative to explore the antitumor activity of this combination in these cohorts.

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Chen et al., 2012, Hodi et al., 2010, Kantoff et al., 2010).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al., 2005, Keir et al., 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer,

breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

In multiple murine tumor models, the interruption of the interaction between PD-L1 and PD-1 resulted in anti-tumor effects (Iwai et al. 2002; Strome et al. 2003). PD-L1 blockade in the syngeneic colorectal cancer model MC-38 (expressing the foreign antigen ovalbumin) resulted in complete responses in all test animals in fewer than 2 weeks of treatment (unpublished Roche data).

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. VEGF is believed to be involved in immune response via the induction of myeloid-derived suppressor cells (MDSCs). These VEGF-induced MDSCs can suppress both T-cell and dendritic-cell function (Gabrilovich 2012). Anti-VEGF therapies may elicit immune responses through diverse mechanisms, including increased trafficking of T cells into tumors (Manning et al. 2007; Shrimali et al. 2010), reduced frequency of MDSC (Kusmartsev et al. 2008), reduction of suppressive cytokines and tumor-infiltrating T regulatory cells and MDSCs (Roland et al. 2009), and increased CD8+ and CD4+ central memory T cells (Hodi et al. 2011).

Collectively, the role of VEGF in the immune response and its critical role in the pathogenesis of multiple malignancies, including several of those in this study, provide a compelling rationale to test whether inhibition of the PD-L1/PD-1 pathway with a human anti−PD-L1 IgG1 effector less antibody with anti-VEGF therapies will result in improved clinical benefit for patients with these diseases.

The safety profile and associated benefit and risk of atezolizumab as a single agent (Phase Ia Study PCD4989g) and in combination with bevacizumab (Phase Ib Study GP28328 and Phase II Study WO29074) support its continued development. In the Phase Ib study of atezolizumab + bevacizumab (Study GP28328), 1 treatment-related grade 3-5 adverse event was observed (Table 1), and the most commonly observed AEs were fatigue, nausea, and pyrexia (Table 2).

Table 1 All Reported Adverse Events in Bevacizumab + Atezolizumab Arm of Study GP28328

Parameter	No (%) of Adverse Events			
	Total		Treatment-Related	
Any adverse event	35	(100.0)	27	(77.1)
Grade 3-5 adverse event	18	(51.4)	1	(2.9)

Serious adverse event	14	(40.0)	0	(0.0)
Adverse event leading to death (Grade 5)	1	(2.9)	0	(0.0)

Table 2 Reported Adverse Events in at least 10% of Patients in Bevacizumab + Atezolizumab Arm of Study GP28328

	No (%) of Adverse Events			
Preferred Term	Total		Treatment-Related	
Any adverse event	35	(100.0)	27	(77.1)
Fatigue	16	(45.7)	7	(20.0)
Nausea	13	(37.1)	7	(20.0)
Pyrexia	13	(37.1)	6	(17.1)
Diarrhea	11	(31.4)	8	(22.9)
Decreased appetite	9	(25.7)	5	(14.3)
Abdominal pain	7	(20)	0	(0.0)
Chills	7	(20.0)	4	(11.4)
Hypertension	7	(20.0)	0	(0.0)
Vomiting	7	(20.0)	2	(5.7)
Cough	6	(17.1)	3	(8.6)
Dyspnoea	6	(17.1)	2	(5.7)
Oedema peripheral	6	(17.1)	0	(0.0)
Upper respiratory tract infection	6	(17.1)	0	(0.0)
Anaemia	5	(14.3)	2	(5.7)
Anxiety	5	(14.3)	0	(0.0)
Epistaxis	5	(14.3)	1	(2.9)

Headache	5 (14.3)	0 (0.0)
Pain in extremity	5 (14.3)	1 (2.9)
Pneumonia	5 (14.3)	0 (0.0)
Pruritus	5 (14.3)	3 (8.6)
Rash	5 (14.3)	3 (8.6)
Arthralgia	4 (11.4)	1 (2.9)
Constipation	4 (11.4)	0 (0.0)
Insomnia	4 (11.4)	0 (0.0)
Productive cough	4 (11.4)	0 (0.0)
Bone pain	3 (8.6)	2 (5.7)
Musculoskeletal pain	3 (8.6)	1 (2.9)

This trial will enroll patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with bevacizumab is expected to be acceptable in this setting.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab when given in combination with bevacizumab (atezo + bev) in patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. Specific objectives and corresponding endpoints for the study are outlined below.

Table 3 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezo + bev	• Objective response (defined as a complete response or partial response on two consecutive occasions ≥ 4

	weeks apart) as determined by a blinded independent radiologist according to RECIST v1.1 (modified RECIST for pleural mesothelioma)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of atezo + bev	• Objective response as determined by an independent radiologist according to immune-modified RECIST • PFS (defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first) as determined by an independent radiologist according to RECIST v1.1 (modified RECIST for pleural mesothelioma). • DOR (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first) as determined by an independent radiologist according to RECIST v1.1 (modified RECIST for pleural mesothelioma) • Disease control as determined by the independent radiology according to RECIST v1.1 (modified RECIST for pleural mesothelioma) • Overall survival, defined as the time from enrollment to death from any cause • PFS as determined by an independent radiologist according to immune-modified RECIST • DoR as determined by an independent radiologist according to immune-modified RECIST • Disease control as determined by the independent radiologist according to immune-modified RECIST
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of atezo + bev	• Occurrence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify biomarkers that are predictive of response to atezo + bev (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to atezo + bev, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, or can increase the	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

knowledge and understanding of disease biology	

DOR = duration of response; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

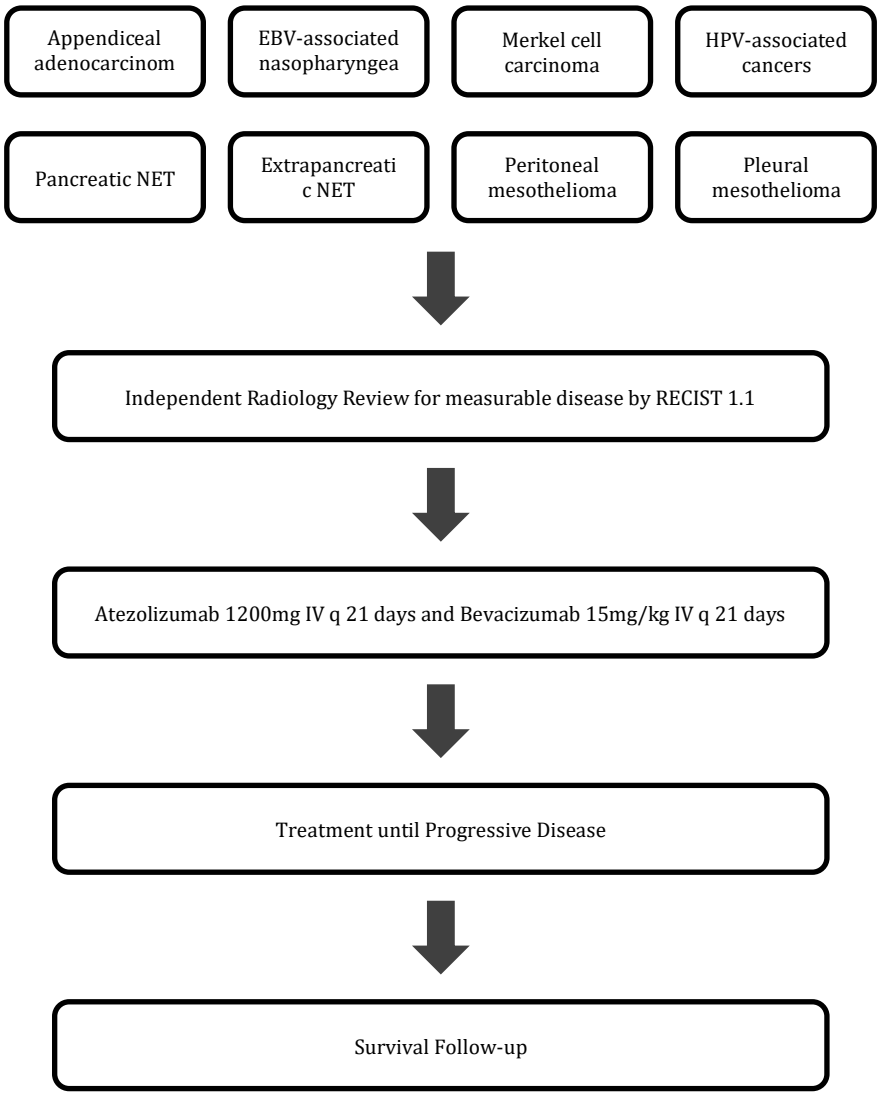
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This study will be a Phase II, single-center, single-arm, open label study evaluating the efficacy and safety of the combination of bevacizumab and atezolizumab in parallel cohorts of patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extrapancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma. The study will enroll approximately 160 patients, with 20 patients in each cohort.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



IV = intravenous; RECIST = Response Evaluation Criteria in Solid Tumors.

Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle and bevacizumab will be administered by intravenous (IV) infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1(modified RECIST for pleural mesothelioma) may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients

who meet criteria for disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) while receiving atezolizumab will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients will undergo tumor assessments by independent radiology review at scheduled intervals during the study (see Section 4.5.5 and Appendix 1 for details).

The expected total length of time on study is anticipated to be approximately 15 months, with 2 weeks spent in screening, 4 weeks in washout, 12 months receiving therapy, and 2 months of follow-up prior to the final protocol visit.

Patients will undergo mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by the investigator, on cycle 2 days 1 and at the time of first evidence of radiographic disease progression according to RECIST v1.1 (modified RECIST for pleural mesothelioma) within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner. These samples will be analyzed to evaluate tumor-infiltrating immune cells [ICs]). In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs, which is expected to be 2 months after the last dose of either agent is administered, given that both atezolizumab and bevacizumab have elimination half-lives of approximately 28 and 21 days, respectively. The end of the study is expected to occur approximately 14 months after the last patient is enrolled. In addition, the PI may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Primary and Secondary Endpoints

The primary endpoint of the study is objective response using RECIST 1.1 (modified RECIST for pleural mesothelioma). Each cohort will be assessed independently, given that each individual disease under study has a distinct natural history. Objective response has long been a standard endpoint in phase II studies seeking preliminary evidence of anti-tumor efficacy, and has been identified as predictive of phase III outcome across tumor types (Oxnard et al., 2016). In pleural mesothelioma, modified RECIST has become standard due to improved quantification of disease burden in the context of a disease more prone to growing along the pleural surface rather than in discrete spheroids.

Secondary endpoints of PFS and OS are accepted assessments of treatment benefit across patient populations, and PFS will be measured using both RECIST 1.1 (modified RECIST for pleural mesothelioma) and irRECIST to permit both accurate reflection of immunotherapy activity and comparison to prior studies.

3.3.2 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) Q3W was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration–to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose. Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg).

3.3.3 Rationale for Patient Population

This study will enroll patients with advanced appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extra pancreatic neuroendocrine tumors, peritoneal mesothelioma, and pleural mesothelioma, regardless of PD-L1 expression.

Each of these advanced cancers remains incurable and life limiting. For nearly all of these tumor types, there is no FDA-approved therapy for the patient population being included in the study. The major exceptions are the neuroendocrine tumor cohorts, where FDA-approved therapy is available, but is frequently deferred in favor of clinical trials of promising agents in appropriately selected patients, given the overall need for additional therapies. Therefore, there remains a continuing need for more efficacious, safe, and better-tolerated treatments for patients with these rare cancers. As discussed in section 1.1, each tumor type has strong preclinical and/or clinical rationale for studying combined PD-L1 and VEGF inhibition to match the unmet need for additional therapies.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 correlates with response to therapy in several, but not all tumor types (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016).

Atezolizumab monotherapy has demonstrated clinical efficacy and is generally well tolerated in patients with other malignancies (Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016). In a Phase II study (GO28753), patients with advanced NSCLC had a significant improvement in OS when treated with atezolizumab compared with docetaxel in the second- or third-line setting (Fehrenbacher et al. 2016).

3.3.4 Rationale for Evaluating Atezolizumab in these Patient Populations

Immune checkpoint inhibitors, including atezolizumab, have demonstrated the potential to deliver significant clinical benefit to patients with advanced cancer (see Section 1.2). In this respect, atezolizumab is an example of an agent that is well tolerated and has the potential to deliver an excellent therapeutic index. In addition, because these therapies have the potential to induce potent anti-tumor immunity, there exists the potential for long-term durable responses.

Each of the diseases under study has significant rationale for studying the impact of immunomodulation. In appendiceal adenocarcinoma, the significant genomic, morphologic, and immunologic similarities to colorectal adenocarcinoma, in which this combination has already shown promise in study GP28328 (NCT01633970). In EBV-associated nasopharyngeal carcinoma, PD-L1 expression and VEGF overexpression are nearly universal, with PD-L1 suppressing the response to EBV (Barber et al., 2006, Fang et al., 2014). PD-1/PD-L1 inhibition has already shown promise in treating HPV-associated squamous cell carcinoma of the anal canal (Morris et al., ASCO 2016), Merkel

cell carcinoma (Nghiem et al., 2016), and mesothelioma (Karim and Leighl, 2016). In neuroendocrine tumors, VEGF inhibition and immunomodulation have both played important roles in the treatment of advanced disease, but the two strategies have never been combined.

3.3.5 Rationale for Evaluating Atezolizumab and Bevacizumab in combination

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggest that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune-cell recruitment to the tumor site (Bouzin et al. 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study of melanoma patients combining an immunomodulatory antibody (anti−CTLA-4; ipilimumab) and bevacizumab (Hodi et al. 2011). In this study of an immunomodulatory agent and bevacizumab, best overall responses were PR in 8 of 22 patients (35%) and stable disease in 6 of 22 patients (27%). All responses were durable for > 6 months. Therefore, the combined treatment with atezolizumab and bevacizumab may augment the antitumor immune response, resulting in improved and more durable clinical benefit.

3.3.6 Rationale for Open-Label Study

An open-label study design was chosen for this trial for a number of reasons. Given the known toxicities associated with immunotherapy, patients assigned to atezolizumab-containing arms, as well as physicians, may be capable of identifying treatment assignment in a blinded study. In addition, a blinded study would require prolonged administration of placebo, which could pose a significant burden to patients. Furthermore, because of the potential for pseudoprogression in patients randomized to atezolizumab-containing arms, a blinded study would require all patients to continue treatment until loss of clinical benefit regardless of whether they were receiving atezolizumab. This could then delay subsequent treatment with approved therapies in patients assigned to the control arm, as well as increase the complexity of treatment decisions.

To ensure the validity of data collected in an open-label study, efficacy analyses will include a supportive analysis based on IRF assessment of progression. In addition, the strategy and timing for final analysis of the primary endpoint, including censoring rules and methods for handling missing data, have been pre-specified in the protocol.

3.3.7 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients to continue treatment after apparent radiographic progression per RECIST v1.1 (modified RECIST for pleural mesothelioma), provided the benefit-risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.1). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status.

3.3.8 Rationale for the Use of Immune-Modified RECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix 4). It is required that radiographic progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression (caused by immune cell infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, use of immune-modified RECIST will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit.

3.3.9 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, after 3 weeks of therapy and at the time of first evidence of radiographic disease progression to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by immune cell infiltration) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T-cell activation, circulating tumor DNA (ctDNA) concentration, and lymphocyte subpopulations may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible, tumor tissue collected at 3 weeks of therapy and at the time of progression will enable NGS and RNA profiling to identify germline and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 160 patients with appendiceal adenocarcinoma, EBV-associated nasopharyngeal carcinoma, HPV-associated cancers, Merkel cell carcinoma, pancreatic neuroendocrine tumors, extra pancreatic neuroendocrine tumors, peritoneal mesothelioma, and peritoneal mesothelioma (20 patients per diagnosis) will be enrolled in this study.

4.1.1 Inclusion Criteria

4.1.1.1 Basket-specific Inclusion Criteria

1. Appendiceal adenocarcinoma
    a. Metastatic appendiceal adenocarcinoma
    b. Not considered candidate for curative surgery

2. Nasopharyngeal carcinoma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Any number of prior therapies, including 0

3. Human Papilloma Virus-associated cancers
    a. Histologically proven squamous carcinoma of the anal canal, penile, vaginal, vulva, or cervical cancer with progression or intolerance to at least one treatment regimen including cisplatin, oxaliplatin or carboplatin will be enrolled. HPV confirmation is not required.
    b. Patients must have metastatic disease not amenable to surgical resection.
    c. If HIV+ positive, all patients infected with Human Immunodeficiency Virus (HIV) and CD4+ T cell count > 400 cells/mm^3 may be eligible for study.
    d. Patients co-infected with hepatitis B virus and/or hepatitis C virus may be included in this study provided that their liver function tests remain within the limits listed above. Patients must be followed by a hepatologist during the course of this study.

4. Merkel Cell Carcinoma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
    c. Any number of prior therapies

5. Neuroendocrine tumors, pancreatic
    a. Grade 1 or grade 2 (or described as low grade, intermediate grade, well differentiated, or moderately differentiated) according to reviewing pathologist
    b. Progressive disease over the preceding 12 months
    c. Any number of prior therapies, including 0
    d. Patients using a somatostatin analogue for symptom control must be on stable doses for 56 days prior to enrollment.

6. Neuroendocrine tumors, extra pancreatic
    a. Grade 1 or grade 2 (or described as low grade, intermediate grade, well differentiated, or moderately differentiated; typical or atypical carcinoid if originating in lung) according to reviewing pathologist
    b. Progressive disease over the preceding 12 months
    c. Any number of prior therapies, including 0
    d. Patients using a somatostatin analogue for symptom control must be on stable doses for 56 days prior to enrollment.

7. Peritoneal mesothelioma
    a. Refractory or intolerant to platinum and pemetrexed systemic therapy
    b. Not considered candidate for curative surgery

8. Pleural mesothelioma
    a. Metastatic or locally recurrent disease not amenable to curative intent treatment
    b. Refractory to platinum and pemetrexed systemic therapy
    c. Any number of prior therapies

4.1.1.2 General Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

  The pleural mesothelioma cohort will require measurable disease according to modified RECIST as specified in the Appendix 5.
- ECOG Performance Status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L without transfusion
  - WBC Count $\geq$ 2500/ul
  - Hemoglobin ≥ 90 g/L

    Patients may be transfused to meet this criterion.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN
  - Serum albumin ≥ 2.5 g/dL
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the last dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea

with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Basket-specific Exclusion Criteria

1. Appendiceal adenocarcinoma
    a. Complete or partial bowel obstruction
2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
    a. none
3. Human Papilloma Virus-associated cancers
    a. None
4. Merkel Cell Carcinoma
    a. none
4. Neuroendocrine tumors, pancreatic
    a. Grade 3, poorly differentiated neuroendocrine carcinoma
    b. Large cell or small cell histology
5. Neuroendocrine tumors, extrapancreatic
    a. Grade 3, poorly differentiated neuroendocrine carcinoma
    b. Large cell or small cell histology
6. Peritoneal mesothelioma
    a. None
7. Pleural mesothelioma
    a. None

4.1.2.2 General Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment for the studied cancer within 28 days prior to initiation of study treatment}
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the bevacizumab formulation

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $<$ 10% of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Positive HIV test at screening (except in cohort 3, HPV-associated cancers)
- Except in cohort 3, HPV-associated cancers, active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test and negative HBV DNA test at screening, are eligible for the study.

- Except in cohort 3, HPV-associated cancers active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study, or up to 5 months following the anticipated last dose of atezolizumab.
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Except for cohort 4, Merkel cell carcinoma, prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

  Patients who received low-dose immunosuppressant medication are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Pregnant or breastfeeding, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg).

  Anti-hypertensive therapy to maintain a systolic blood pressure <150 mmHg and/or

diastolic blood pressure < 100 mmHg is permitted.

- Prior history of hypertensive crisis or hypertensive encephalopathy
- History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
- Patients with a baseline ECG demonstrating a QTc > 460 ms
- Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 calendar days prior to Cycle 1, Day 1) use of dipyramidole, ticlopidine, clopidogrel, or cilostazol.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
- Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or > 1.0 g of protein in a 24-hour urine collection

  All patients with $\geqslant$ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Treatment with the combination of atezolizumab and bevacizumab will be administered to all patients in an open-label, unblinded fashion. Patients will be assigned to cohorts based on tumor histology as assessed by an MD Anderson Cancer Center pathologist.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are atezolizumab and bevacizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

Atezolizumab will be supplied by Genentech Inc as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

Atezolizumab may be prepared, handled, and administered per the current FDA-approved package insert.

4.3.1.2 Bevacizumab

Bevacizumab will be supplied by the Genentech Inc of Basel, Switzerland as a clear-to-slightly-opalescent, sterile liquid ready for parenteral administration. Each 400-mg (25-mg/mL) glass vial contains 16 mL of bevacizumab (25 mg/mL) with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only. For further details, see the Bevacizumab Investigator's Brochure.

Bevacizumab is intended for use solely in clinical trials. The drug provided for clinical trial use is expected to be very similar in safety and activity to the commercially marketed drug (Avastin®).

Bevacizumab may be prepared, handled, and administered per the current FDA-approved package insert.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of any of the study treatments should be noted on the electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Atezolizumab will be administered prior to bevacizumab, with a minimum of 5 minutes between dosing.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±5) minutes after the infusion.

Refer to the FDA-approved package inserts for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.3 and in the Atezolizumab Investigator's Brochure.

4.3.2.2 Bevacizumab

The dose of bevacizumab in this study is 15 mg/kg administered by IV infusion every 3 weeks on Day 1 each 21-day cycle. The interval between infusions must not be < 10 days. The bevacizumab dose will be based on the patient’s weight at enrollment and will remain the same throughout the study unless there is a weight change of > 10% from baseline. It is not necessary to correct dosing based on ideal weight, unless warranted per institutional guidelines/standard.

The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The patient should be

observed for at least 2 hours after the first administration of the combination and for 1 hour (± 30 minutes) for subsequent infusions.

If a patient experiences an infusion-associated adverse event, he or she may be pre-medicated for the next bevacizumab infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes as long as the patient continues to be pre-medicated. If a patient experiences a second episode of an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 (± 15) minutes. Similarly, if a patient experiences a second episode of an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 (± 10) minutes.

Upon receipt of the bevacizumab, vials are to be refrigerated at 2°C−8°C (36°F−46°F) and should remain refrigerated until use. Vials should be protected from light. DO NOT FREEZE. DO NOT SHAKE. VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab and bevacizumab) will be provided by the Genentech Inc where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Genentech Inc with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Genentech Inc. The site must obtain written authorization from the Genentech Inc before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded in the electronic medical record.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 7).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, except as outlined below.

  After Cycle 1, Day 14, palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and bevacizumab may be continued during palliative radiotherapy.

  Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Re-screening is required if a patient has not met all of the eligibility criteria within 28 days from the original date of the screening visit. Re-screening refers to repeating the entire screening process with the exception of performing a repeat biopsy to collect a tumor tissue sample to be used to determine PD-L1 status and repeating CT and/or MRI imaging scans used for tumor assessment, provided the biopsy tissue sample and imaging scans were obtained during the original screening visit. Patients are only allowed to be re-screened twice. Blood samples may be redrawn due to sample handling problems, breakage, or sample integrity, without being considered a re-screen.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the

cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Height will be assessed at baseline, and weight will be assessed at each study visit.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and every 9-12 (± 1) weeks thereafter (with neuroendocrine cohorts 5 and 6 assessed every 12 weeks and all other cohorts assessed every 9 weeks), regardless of dose delays, until radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) or (for atezolizumab-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Cross sectional imaging will be performed with either contrast enhanced CT or MRI. RECIST 1.1 (modified RECIST for pleural mesothelioma) criteria will be used to determine disease response.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Response will be assessed by an independent, blinded radiologist at the MD Anderson Quantitative Imaging Analysis Core using RECIST v1.1 (see Appendix 3) and immune-modified RECIST (see Appendix 4). Pleural Mesothelioma will use modified RECIST as in the Appendix 5. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Genentech Inc for analysis:

- Blood samples for exploratory research on biomarkers
- Fresh tumor tissue sample collected at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

  Tissue should be collected by excisional or core needle biopsy, typically using a 21-18 gauge needle. The biopsy should include at least 5 cores, 2 FFPE and 3 fresh frozen. It should be collected within 28 days prior to initiation of protocol therapy.
- Tumor tissue sample collected at week 3 and at time of progression for exploratory research on biomarkers

  Biopsies at week 3 should be performed within 7 days before or after the administration of C2D1 of study therapy (with prior to therapy preferred). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, immunohistochemistry for PD-L1, multiplexed immunofluorescence for immune markers, flow cytometry, analysis of ctDNA concentration, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of germline or somatic mutations, and use of WGS or NGS.

For the neuroendocrine tumor cohorts, exploratory biomarkers will also include antibody titers to GAD and IA-2, assessed at baseline and after 3 weeks of treatment.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final manuscript has been completed, with the following exceptions:

- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Blood, plasma, serum, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final manuscript has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to patients unless required by law.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible.

Patients receiving bevacizumab should be carefully monitored for clinical signs and symptoms of congestive heart failure, especially in patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF should also be considered (echocardiogram or MUGA).

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Mandatory Samples for Whole Genome Sequencing

Blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) to identify germline or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research and the WGS portion of the Informed Consent Form by the Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in

aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from WGS specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Genentech, Inc. policy on study data publication.

4.5.8.1 Guidelines for Return of Incidental Results:

The decision-making for return of incidental results will be made as approved by the MD Anderson Cancer Center IRB in protocol PA12-1099 and described herein: Return of incidental results guidelines are being generated for common genetic alterations by a Return of Results Committee via Consultation between Institute of Personalized Cancer Therapy, Clinical Cancer Genetics, Molecular Diagnostic Laboratory, and Behavioral Science. Rarer alterations will be discussed on a case by case basis by the Return of Results Committee with input from Clinical Cancer Genetics, and selected cases will be discussed in person or virtually in the Molecular Tumor Board. The treating investigator will initiate return of results with genetic counseling based on recommendations of the Return of Results Committee. We will be initially reporting cancer-related genes only and only those that are clearly deleterious and actionable; we will expand our reporting to non-cancer related risk genes as we establish expertise in genetic counseling in this arena. This reporting will be congruent with the IRB-approved guidance for reporting of such results.

Patients with deleterious germline alterations who are alive but not under MD Anderson care will be contacted by treating investigator after discussion of the alteration in return of results committee and validation of the alteration in an anonymized fashion.

Genetic alterations will be considered to have “clinical utility” if the genetic risk associated with the variant is well-recognized and significant. Variants for which there would be clinical implications such as change in screening, chemoprevention or other behavior change, change in therapy or drug dose will be considered to have clinical utility. Variants that confer a high disease risk and that can be reduced by prevention/therapy would be especially prioritized for return.

We will initially consider return of results on cancer-related genes felt to have clinical utility. Please refer to protocol PA12-1099 for genes that are currently tested by our clinical cancer genetics program, as well as other cancer-related genes that may have clinical utility. These genes will be prioritized for discussion in the Return of Results Committee, and alterations in these genes will be specifically considered for return to patients with appropriate genetic counseling and CLIA validation. Notably, the actionability or clinical utility of any particular variant within a gene will also depend upon the pathogenicity of that variant as determined by the lab’s interpretation (e.g. polymorphism, low-penetrance susceptibility, variant of unknown significance, deleterious mutation associated with hereditary cancer). Examples of this include germline MET T1010I vs. MET mutations causative of hereditary papillary renal cancer, and APC I1307K vs. APC mutations causing FAP.

If an alteration is determined to have clinical utility based on guidelines developed, or based on assessment by the Return of Results Committee and/or by Clinical Cancer Genetics or by discussion at Molecular Tumor Board, next the alteration would be validated in a CLIA validated laboratory, in anonymized fashion, when possible. For cancer-related genes, this testing will be done using a unique “study identifier” rather than “patient identifiers” to protect the patient’s privacy. The testing may be outsourced to Medical Genetics Laboratories at Baylor, Myriad Genetics Illumina, Invitrae, Ambry, Guardant, Genomic Health, Broad Institute, Life Technologies/ThermoFisher, Complete Genomics etc. If MD Anderson develops CLIA tests for these alterations in the future, they may be done at MD Anderson. After confirmation of the alteration in a CLIA lab, patient will be contacted. The testing may identify conditions for which genetic counseling and germline testing in the CLIA environment is frequently facilitated in our institution (e.g. BRCA testing). If sample is not available for validation in a CLIA lab, results felt to be deleterious and high confidence as assessed by the Return of Incidental Results Committee may be returned to the patient without additional testing. Notably, to date all deleterious germline validations identified were successfully validated on a separate CLIA assay. For these alterations, the patient will be contacted by the treating investigator or genetic counselor, and invited for formal genetic counseling. Standard clinical counseling and CLIA testing will then be recommended for at-risk family members. Of note, in some unfortunate cases the patient may be deceased when the results of genomic testing become available, and the patient’s designated power of attorney will be contacted instead.

Return of incidental results to patients by the investigator or clinical cancer genetics team will be documented either with a telephone note or a clinic note.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab and bevacizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma), with the following exception:

  Atezolizumab-treated patients will be permitted to continue study treatment after experiencing radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) if they meet all of the following criteria:

  – Evidence of clinical benefit, as determined by the investigator following a review of all available data
  – Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
  – Absence of decline in ECOG Performance Status that can be attributed to disease progression
  – Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit $\leq$30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or Genentech, Inc. terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination
- Patient non-adherence to the study plan as determined by the investigator

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The PI has the right to terminate this study and one or more cohorts in the study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1 and 5.1.2). Guidelines for management of patients who experience specific adverse events are provided in Table 5 (see Section 5.1.3.3).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs, immune-related hepatitis, pneumonitis, nephritis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis. In addition, systemic immune activation (described below) is a potential risk associated with atezolizumab. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the PI for additional recommendations.

5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: hypertension, proteinuria, venous thromboembolism, arterial thromboembolism, gastrointestinal perforation, fistula, wound healing complications, hemorrhage, mucocutaneous hemorrhage, posterior reversible leukoencephalopathy, systolic heart failure, ovarian failure, neutropenia, and hypersensitivity and infusion reactions. Please refer to section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for bevacizumab.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The bevacizumab dose will be based on the patient's weight at enrollment and will remain the same throughout the study, unless there is a weight change of > 10% from baseline. It is not necessary to correct dosing on the basis of ideal weight, unless warranted per institutional guidelines/standard. Management of bevacizumab may be performed according to the label.

5.1.3.2 Treatment Interruption

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 105 days, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 105 days if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Patients who discontinue atezolizumab either transiently or permanently (e.g., for adverse events) may continue on bevacizumab until disease progression if there is felt to be clinical benefit.

Patients who discontinue bevacizumab transiently or permanently for adverse events may continue on single-agent atezolizumab until disease progression if there is felt to be clinical benefit. Patients with Grade ≥ 3 toxicities attributable to bevacizumab should withhold atezolizumab until those toxicities have improved to Grade ≤ 2 (exception for Grade 3 hypertension). If bevacizumab is permanently discontinued but there is felt to be clinical benefit from atezolizumab, the latter may be continued.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. Patients who develop Grade 4 toxicities related to bevacizumab for > 21 days should permanently discontinue bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab should occur ≥ 28 days after surgery and after wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

Bevacizumab infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

5.1.3.3 Management Guidelines

Guidelines for management of patients who experience specific adverse events are provided in Table 5.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Atezolizumab:	
Anaphylaxis	• For anaphylaxis precautions, see Appendix 7.
IRRs	
Atezolizumab infusion-related reaction, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Interrupt or slow the rate of atezolizumab infusion • Continue bevacizumab.
Atezolizumab infusion-related reaction, Grade 3 or 4	• Permanently discontinue atezolizumab • Continue bevacizumab
Pulmonary events	
Pneumonitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pneumonitis, Grade 2	• Hold atezolizumab until resolution • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. If not, permanently discontinue bevacizumab. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.

Event	Action to Be Taken
Pneumonitis, Grade 3 or 4	• Permanently discontinue atezolizumab • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper. • Permanently discontinue bevacizumab.
Hepatotoxicity	
Immune-mediated hepatitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Immune-mediated hepatitis, Grade 2	• Hold atezolizumab until resolution • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper, for grade 2 elevation of transaminases, with or without bilirubin elevation. **Events of > 5 days' duration:** • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Immune-mediated hepatitis, Grade 3 or 4	• Permanently discontinue atezolizumab • Administer steroids at 1-2 mg/kg/day prednisone equivalents, followed by corticosteroid taper • Permanently discontinue bevacizumab.
Hepatic event, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Hepatic event, Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. **Events of > 5 days' duration:** • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Hepatic event, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.
Gastrointestinal toxicity	
Diarrhea or colitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.

Event	Action to Be Taken
Diarrhea or colitis, Grade 2	• Hold atezolizumab • If symptoms persist for longer than 5 days or recur, administer 1-2mg/mg/day prednisone equivalent • When symptoms resolve to Grade 0 or 1, taper corticosteroids over at least 1 month • Resume treatment with atezolizumab if the event resolves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg/day oral prednisone or less. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diarrhea or colitis, Grade 3	• Hold atezolizumab • Administer 1-2mg/mg/day IV methylprednisolone • When symptoms resolve to Grade 0 or 1, taper corticosteroids over at least 1 month • Resume treatment with atezolizumab if the event resolves to grade 0 or 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10 mg/day oral prednisone or less. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Endocrine disorders	
Hypophysitis, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab
Hypophysitis, Grade 2 or 3	• Withhold atezolizumab • Administer corticosteroids and hormone replacement as clinically indicated • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Hypophysitis, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.

Event	Action to Be Taken
Asymptomatic hypothyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Symptomatic hypothyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab and begin thyroid replacement therapy as needed • Isolated hypothyroidism should be managed with replacement therapy and without corticosteroids • Resume atezolizumab when symptoms are controlled and thyroid function is improving • Withhold bevacizumab. • Resume bevacizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab and initiate an anti-thyroid drug as indicated. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Withhold bevacizumab. • Resume bevacizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue bevacizumab for life-threatening immune-related hyperthyroidism.

Event	Action to Be Taken
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once symptoms resolve. • Taper corticosteroids over at least 1 months when symptoms improve to Grade 0 or 1. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone, and the patient is stable on replacement therapy. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Diabetes Mellitus, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Initiate treatment with insulin for type I diabetes mellitus • Continue bevacizumab.
Diabetes Mellitus, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Resume atezolizumab when metabolic control is achieved on insulin replacement therapy. • Withhold bevacizumab. • Resume bevacizumab when symptoms resolve and glucose levels are stable.
Ocular toxicity	
Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab. • If symptoms persist, treat as a Grade 2 event.
Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.

Event	Action to Be Taken
Pancreatic toxicity	
Amylase and/or lipase elevation, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Amylase or lipase elevation, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks, and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue bevacizumab.
Immune-related pancreatitis, Grade 2 or 3	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks, symptoms of pancreatitis have resolved, and corticosteroids have been reduced to the equivalent of up to 10mg/day oral prednisone. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue bevacizumab.
Immune-related pancreatitis, Grade 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Recurrent pancreatitis of any grade is to be considered a grade 4 event. • Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Infection	

Event	Action to Be Taken
Infection, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Follow guidelines provided in the Bevacizumab Package Insert and Investigator's Brochure.
Infection, Grade 3	• Withhold atezolizumab • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. • Withhold bevacizumab • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Infection, Grade 4	• Permanently discontinue atezolizumab • Permanently discontinue bevacizumab.
Dermatologic toxicity	
Rash, Grade 1 or 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.
Rash, Grade 3	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks.
Rash, Grade 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue bevacizumab.
Neurologic disorders	
Immune-related neuropathy, Grade 1	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Continue bevacizumab.

Event	Action to Be Taken
Immune-related neuropathy, Grade 2	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Withhold atezolizumab. • Institute medical intervention as appropriate • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks • Withhold bevacizumab. • Resume bevacizumab if event resolves to Grade 1 or better within 12 weeks. • Permanently discontinue bevacizumab if event does not resolve to Grade 1 or better within 12 weeks
Immune-related neuropathy, Grade 3 or 4	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Institute medical intervention as appropriate • Permanently discontinue bevacizumab.
Myasthenia gravis and Guillain-Barré, all grades	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Institute medical intervention as appropriate • Consider initiation of systemic corticosteroids at a dose of 1-2mg/kg/day oral prednisone. • Permanently discontinue bevacizumab.
Immune-related meningitis or encephalitis, all grades	• Follow guidelines provided in the Atezolizumab Package Insert and Investigator's Brochure. • Permanently discontinue atezolizumab. • Administer methylprednisolone 1-2mg/kg/day IV followed by oral prednisone 1-2mg/kg/day or equivalent once the patient improves. • Taper corticosteroids over at least 1 months when symptoms improve to Grade 0 or 1. • Permanently discontinue bevacizumab.
Nephritis	
Nephritis, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.

Event	Action to Be Taken
Nephritis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Nephritis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Bevacizumab: **Hypertension**	
Grade 1	No dose modification
Grade 2	• Withhold bevacizumab. Start antihypertensive therapy per institutional policy. Patient may resume bevacizumab after blood pressure < 150/90 mmHg.
Grade 3	• Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	• Discontinue bevacizumab
Hemorrhage	
Grade 1 or 2, non-CNS, non-pulmonary events	• No bevacizumab modification
Grade 3 non-CNS, non-pulmonary events	• Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. • Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab.

Event	Action to Be Taken
Grade 4 non-CNS, non-pulmonary events	• Discontinue bevacizumab
Grade 1 pulmonary events	• Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary events	• Discontinue bevacizumab
CNS hemorrhage, any grade	• Discontinue bevacizumab
Venous thromboembolism	
Grade 1 or 2	• No bevacizumab modification
Grade 3 or asymptomatic Grade 4	• If the planned duration of full-dose anticoagulation is < 2 weeks bevacizumab should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	• Discontinue bevacizumab
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	• Discontinue bevacizumab permanently.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
Grade 1 or 2	• No bevacizumab modification
Grade 3	• Withhold bevacizumab until resolution to Grade $\leqslant$ 1.
Grade 4	• Discontinue bevacizumab.
Proteinuria	
Grade 1 (urine dipstick 1^+ or urine collection 0.15 to 1.0 g/24 hr)	• No bevacizumab modification

Event	Action to Be Taken
Grade 2 (urine dipstick 2^+-3^+ or urine collection >1.0 to to 3.5 g/24 hr)	• For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose. • For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab. • Withhold bevacizumab for proteinuria > 2 g/24hr and resume when proteinuria is $\leqslant$ 2 g/24hr.
Grade 3 (urine dipstick 4^+ or urine collection > 3.5 g/24 hr)	• Withhold bevacizumab. • Resume bevacizumab when proteinuria $\leqslant$ 2g/24h[a]
Grade 4 (nephrotic syndrome)	• Discontinue bevacizumab.
GI Perforation	
Any grade	• Discontinue bevacizumab.
Fistula	
Any grade tracheoesophageal fistula	• Discontinue bevacizumab.
Grade 4 fistula (other than tracheoesophegeal)	• Discontinue bevacizumab.
Bowel Obstruction	
Grade 1	• Continue bevacizumab for partial obstruction not requiring medical intevervention.
Grade $\geqslant$ 2	• Discontinue bevacizumab.
Wound Dehiscence	
Any grade	• Discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy	
Any grade	• Discontinue bevacizumab.

IRR = infusion-related reaction; TSH = thyroid-stimulating hormone.

[a] All proteinuria values are from 24-hour urine collections

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor and to Genentech Inc, as outlined in Section 5.4.

5.2.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Genentech Inc products, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Adverse events may occur during the course of the use of Genentech Inc products in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events (regardless of grade or attribution) that occur after the consent form is signed but before treatment initiation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment initiation through 90 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 5.3. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to Genentech Inc)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

Adverse Events of Special Interest (Immediately Reportable to the Sponsor and Genentech Inc)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Atezolizumab AEs of Special Interest

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Bevacizumab AEs of Special Interest

- Hypertension ≥ grade 3

- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (or RPLS; any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ⩾ grade 2

5.2.3 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Immune-mediated adverse events, including conditions (regardless of grade) suggestive of an autoimmune disorder, such as Grade ≥ 3 rash or pruritus, Grade ≥ 3 diarrhea or Grade ≥ 2 colitis.

Cases of potential drug-induced liver injury that include Grade ≥ 3 asymptomatic AST/ALT/total bilirubin elevations, or Grade ≥ 2 AST/ALT/total bilirubin elevations with constitutional symptoms (Hy's law, see Section 5.3.5.6)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor and Genentech Inc in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events (all grades and attributions), whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v 4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The PI or designee will be responsible for assigning attribution of adverse events to the study agent.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms

cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the underlying malignancy should be recorded on the eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor and Genentech Inc (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the

cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Deaths that occur after the adverse eventreporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Underlying Malignancy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1 criteria (modified RECIST for pleural mesothelioma). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR AND GENENTECH INC

Certain events require immediate reporting to allow the Sponsor and Genentech Inc to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor and Genentech Inc immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor and Genentech Inc within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (see Section 5.4.1 for further details)
- Adverse events of special interest (see Section 5.4.1 for further details)
- Pregnancies (see Section 5.4.2 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

For reporting of adverse events to Genentech, Inc., reports should be faxed to GNE fax number (650) 238-6067 or sent via email to usds_aereporting-d@gene.com.

5.4.1 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.1.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment (or until initiation of new systemic anti-cancer therapy, whichever occurs first). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$90 days after the last dose of study treatment are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.2.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor and Genentech Inc or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

5.4.2.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.2.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor and Genentech Inc immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Supporter Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, Genentech Inc or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The PI or designee will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the PI or designee will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Bevacizumab Investigator's Brochure

The PI or designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a phase II study to assess the efficacy of atezolizumab combined with bevacizumab in 8 rare solid tumor groups:

1. Appendiceal adenocarcinoma, KRAS-wild type
2. Epstein-Barr Virus-associated nasopharyngeal carcinoma
3. Human Papilloma Virus-associated cancers
4. Merkel cell carcinoma
5. Neuroendocrine tumors, pancreatic
6. Neuroendocrine tumors, extrapancreatic
7. Peritoneal mesothelioma
8. Pleural mesothelioma

The primary endpoint is the overall best response since the start of the treatment. A total of 136 patients will be enrolled, i.e., 20 patients in each tumor group, except for Cohort 2, nasopharyngeal carcinoma, which will be terminated after 4 patients are enrolled, and Cohort 4, Merkel cell carcinoma, which will be terminated after 12 patients have been enrolled. Considering the rarity of the diseases, the patient accrual rate is approximately 1 to 2 patients per month per tumor group. And the total duration of the study will be up to 30 months.

6.1 DETERMINATION OF SAMPLE SIZE

For each tumor group, we will estimate the best response rate and its 95% confidence interval (CI). When the sample size is 20, and the response rate is 0.3, the two-sided 95% exact confidence interval using the Clopper and Pearson method will be (0.119, 0.543). The exact 95% CI is calculated for various scenarios of true best response rate in Table 9.

Table 8 The exact 95% CI is calculated for various scenarios of true best response rate

Sample Size (N)	Best response rate	95% exact CI
20	0.3	(0.119, 0.543)
20	0.2	(0.057, 0.437)
20	0.1	(0.012, 0.317)

The table below lists the response rate p_0 based on the historical data for each group.

Table 9 The best response rate based on historical data

	Tumor Type	p_0
1	Appendiceal adenocarcinoma, KRAS-wild type	1%
2	Epstein-Barr Virus-associated nasopharyngeal carcinoma	10%
3	Human Papilloma Virus-associated cancers	5%
4	Merkel cell carcinoma	5%
5	Neuroendocrine tumors, pancreatic	10%
6	Neuroendocrine tumors, extrapancreatic	5%
7	Peritoneal mesothelioma	1%
8	Pleural mesothelioma	5%

6.2 SUMMARIES OF CONDUCT OF STUDY

This is a basket trial of eight parallel phase II trials of the combination of Atezolizumab and Bevacizumab in rare cancer patients. Enrollment, study drug administration, and discontinuation from the study will be summarized by all patients and tumor group. The reasons for study drug discontinuation will be also tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by tumor group.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographic information (e.g. age, gender) at baseline will be analyzed, with data summarized in mean ± standard deviation, median and range for continuous variables, and in frequency count and percentage for categorical variables. The student t-test or the Wilcoxon test may be used to compare continuous variables among different tumor patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all patients who received at least one dose of the study drug.

6.4.1 Primary Efficacy Endpoint

The primary outcome is the overall best response rate (PR or CR) since the start of treatment, with the primary analysis performed no less than six months after the final patient is enrolled. For each tumor group, we will estimate the best response rate and its 95% exact confidence interval using the Clopper and Pearson method. And we will assess the efficacy of the combination treatment by performing the independent binomial test comparing the best response rate versus the historical control for each tumor group. Considering the limited sample size for each tumor group, we may apply the Bayesian classification and information sharing method proposed by Lee and Chen (submitted) in the data analysis. It will provide a more efficient and more powerful way to estimate and test the response rate for similarly performed groups. We will first cluster the tumor groups according to their response rate into the low- or high-response cluster first, and then apply the Bayesian hierarchical model to borrow information among groups within the same cluster in estimating their response rate and comparing it to the historical control.

6.4.2 Secondary Efficacy Endpoints

For each tumor group, median DOR and corresponding 2-sided 95% CI will be reported.

Time-to-event outcomes, including progression free survival (PFS) and overall survival (OS), will be estimated using Kaplan-Meier method. Patients discontinuing treatment for reasons other than toxicity (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination, or death, whichever occurs first. Patients who discontinue study treatment for reasons other than withdrawal of consent will be followed for survival and subsequent ant-cancer therapies approximately every 3 months until death, loss to follow–up, withdrawal of consent, or study termination. During this period, documentation of anti-cancer therapies should include administration start and stop dates. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model may be utilized to include multiple covariates in the time-to-event analysis.

6.4.3 Exploratory Efficacy Endpoints

Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each tumor group. The time-course of biomarker measures will be investigated graphically. If there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic

regression will be used to explore possible associations between biomarker measures and clinical outcomes.

6.5 SAFETY ANALYSES

The safety analyses will include all patients who received at least one dose of study treatment, with patients grouped according to treatment received.

Verbatim adverse events and severity will be graded according to NCI CTCAE v4.0.

The safety analyses will include all patients who received at least one dose of study treatment. Toxicity data will be summarized by frequency tables for each tumor type group. The association between the types and severity of toxicity and the tumor group will be evaluated. No formal statistical testing will be performed on these summaries.

6.6 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with treatment response, including efficacy and/or adverse events. Biomarker analyses may be reported in a separate report.

6.7 INTERIM ANALYSES

6.7.1 Interim Safety Monitoring

For patient safety, A Bayesian toxicity monitoring rule will be implemented for the treatment related toxicity events during the duration of the treatment in all treated patients across 8 tumor groups.

A toxicity event is defined as:

---All non-hematologic AEs Grade $\geqslant$ 3 with the exceptions of:

- Grade 3 Hypertension
- Grade 3 Nausea
- Grade ≥ 3 Diarrhea if reversible within 48 hours with maximal supportive care
- Electrolyte abnormalities that are reversible within 72 hours with supportive care and/or supplementation

---All hematologic AEs Grade $\geqslant$ 4

---Pneumonitis
---Colitis
---Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism or hypophysitis
---Hepatitis, defined as AST or ALT $>10\times$ ULN
---Systemic lupus erythematosus
---Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
---Hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, or systemic immune activation

---Nephritis
---Ocular toxicities (e.g. uveitis, retinitis)
---Myositis
---Myopathies, including rhabdomyolysis
---Grade ≥2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
---GI perforation, abscesses and fistulae (any grade)
---CNS bleeding
---Haemoptysis ≥ grade 2
---Arterial thromboembolic events (any grade)
---PRES (or RPLS; any grade)
---Non-GI fistula or abscess ⩾ grade 2

Let p.tox be the toxicity probability, then if Pr [p. tox > 0.3] >0.9, we will terminate the study early. The protocol statistician will apply the monitoring every 5 patients for the first 20 patients, then every 10 for the rest of study. That is, we will early stop the study if we observe [# patients experiencing toxicity] / [#patients being treated] >= 4/5, 6/10, 8/15, 9/20, 13/30, 16/40, 20/50, 23/60, 27/70, 30/80, 33/90, 37/100, 40/110, 43/120, 46/130, 50/140, 53/150, or 56/160. The operating characteristic for applying this toxicity monitoring rule is shown in the table below.

Table 10 Operating characteristics for toxicity early stopping based 5000 simulation runs per scenario

True toxicity probability	Early stopping probability	Average sample size
0.2	0.021	157.0
0.3	0.317	123.8
0.4	0.950	47.1
0.5	0.999	19.1

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The University of Texas MD Anderson Cancer Center will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. The PI will perform oversight of the data management of this study.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at The University of Texas MD Anderson Cancer Center and records retention for the study data will be consistent with The University of Texas MD Anderson Cancer Center's standard procedures, which mandate that data be maintained indefinitely.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of the MD Anderson Cancer Center Prometheus EDC system.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

SAE data will be captured via eSAE in accordance with Sponsor policy.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that

shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator indefinitely, in accordance with the current policy of the MD Anderson Cancer Center IND office.

Written notification should be provided to the Sponsor and Genentech Inc prior to transferring any records to another party or moving them to another location.

7.6 MONITORING

During the study, a study monitor from the University of Texas MD Anderson Cancer Center Investigational New Drug Office will have regular contacts with the investigator and team.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a

patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor and Genentech Inc with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol

amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

The Investigator is responsible for completing the cohort summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 5 evaluable patients, and every 5 evaluable patients, thereafter.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and Genentech Inc and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 ADMINISTRATIVE STRUCTURE

This trial will be supported via the rare disease strategic alliance between The University of Texas MD Anderson Cancer Center and Genentech. The University of Texas MD Anderson Cancer Center will be the sole site, responsible for enrolling approximately 160 total patients.

The MD Anderson Cancer Center IND office will provide oversight of safety (see Section 5.2).

After written informed consent has been obtained, the study team will generate a unique study identification number for the patient.

Patient data will be recorded via an EDC system with use of eCRFs.

Central laboratories, including those at Genentech/Roche/Roche collaborators and at The University of Texas MD Anderson Cancer Center, will be used for PD-L1 expression status determination and will provide kits for pharmacogenomic, tissue, whole blood, serum, and plasma sample analyses to be conducted at central laboratories or Genentech.

Treatment decisions will be made on the basis of the local reading of ECGs obtained during the study.

Imaging data will be retained at The University of Texas MD Anderson Cancer Center.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor and Genentech Inc is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all

requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to Genentech Inc prior to submission for publication or presentation. This allows Genentech Inc to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Genentech Inc will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Genentech Inc personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Genentech Inc personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Genentech Inc, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in contact information).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol 2012;30:507–12.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634–46.

DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277–80.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. 2012 Dec. EMA/CHPM/205/95/Rev.4.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Fozza C, Corda G, Virdis P, et al. Derangement of the T-cell repertoire in patients with B-cell non–Hodgkin's lymphoma. Eur J Haematol 2014:1–12.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. J Clin Oncol 2006;24:5545–51.

[FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007 May.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression-free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. BMJ Open 2013;3:1–6.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;12:528–38.

Postow M, Manuel M, Wong P, et al. T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma. J Immunother Cancer 2014;2(Suppl 3):08.

Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a atezolizumab study. J Clin Oncol 2013;31:abstract 3001.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12):2367–75.

Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006;355:2542–50.

Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 2010;11:861–70.

Stinchcombe TE, Socinski MA, Lee CB, et al. Considerations for second-line therapy of non-small cell lung cancer. Oncologist 2008;13:128–36.

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. New Engl J Med 2010;363:733–42.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Appendix 1

Schedule of Activities

	Screening [a]	Odd Treatment Cycles (21-day cycles)	Cycle 1 only	Even Treatment Cycles (21-day cycles)	Cycle 2 only	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±7 days)	Day 8 (±3 days)	Day 1 (±7 days)	Day 8 (±3 days)	≤30 Days after Last Dose	
Informed consent	x [c]						
Demographic data	x						
Medical history and baseline conditions	x						
Vital signs [e]	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	
Height	x						
Complete physical examination [f]	x					x	
Limited physical examination [g]		x	x	x	x		
ECOG Performance Status	x	x	x	x	x	x	
ECG [h]	x						
Hematology [i]	x [j]	x [k]	x	x	x	x	
Chemistry [l]	x [j]	x [k]	x	x	x	x	

Appendix 1
Schedule of Activities (cont.)

	Screening [a]	Odd Treatment Cycles (21-day cycles)	Cycle 1 only	Even Treatment Cycles (21-day cycles)	Cycle 2 only	Treatment Discontinuation [b]	Follow-Up
	Days –28 to –1	Day 1 (±7 days)	Day 8 (±3 days)	Day 1 (±7 days)	Day 8 (±3 days)	≤30 Days after Last Dose	
Pregnancy test [m]	x [j]						
Coagulation (INR, aPTT)	x [j]					x	
TSH, free T3 (or total T3 [n]), free T4	x [j]	x [n]				x	
Viral serology [o]	x [j]						
Urinalysis [p]	x [j]	x [q]					
Echo/MUGA	x [r]	x [r]		x [r]			
Blood sample for biomarkers	x [s]			x [s]		x [s]	x [s]
Blood sample for WGS	x						
Tumor biopsy (if clinically feasible)	x			X [t]		X [u]	
Tumor response assessments	x [v]	x [w,x]		x [w,x]			
Concomitant medications [y]	x [y]	x	x	x	x	x	
Adverse events [z]	x [z]	x [z]	x [z]	x [z]	x [z]	x	x [z]
Study treatment administration [aa]		x		x			
Survival follow-up and anti-cancer treatment							x [bb]

Appendix 1
Schedule of Activities (cont.)

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 30 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] A pretreatment tumor biopsy is required.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline on the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[j] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.

[m] All women of childbearing potential will have a serum pregnancy test at screening.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter.

Appendix 1
Schedule of Activities (cont.)

[o] At screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[q] Urinalysis should be performed every 6 weeks (2 cycles) during study treatment.

[r] Echo or MUGA to be considered at baseline and thereafter per clinical suspicion

[s] See Appendix 2 for detailed schedule.

[t] On-treatment biopsy will be obtained on Cycle 2 Day 1, +/- 7 days (prior to C2D1 preferred)

[u] Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.

[v] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 (modified RECIST for pleural mesothelioma) may be used.

[w] Patients will undergo tumor assessments at baseline and every 9-12 weeks thereafter (with neuroendocrine cohorts 5 and 6 assessed every 12 weeks and all other cohorts assessed every 9 weeks), regardless of dose delays, until radiographic disease progression per RECIST v1.1 (modified RECIST for pleural mesothelioma) or (for atezolizumab-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Appendix 1
Schedule of Activities (cont.)

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor and Genentech Inc should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[aa] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day −28 to Day –1)	NA	Biomarker (blood, plasma, and serum) In cohorts 5 and 6 (neuroendocrine tumors), antibody titers to GAD and IA-2 will be assessed in the CLIA environment.
Day 1 of Cycle 2	Prior to infusion	Biomarker (blood, plasma, and serum) In cohorts 5 and 6 (neuroendocrine tumors), antibody titers to GAD and IA-2 will be assessed in the CLIA environment.
Progression (≤ 40 days after progression is radiographically determined[j])	NA	Biomarker (blood, plasma, and serum)

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥ 10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be

taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm)

should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to <10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Tables 1–3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 4
Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥ 30% decrease in tumor burden, [a] in the absence of CR
PD	≥ 20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥ 20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 mm but $<$15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

<u>ASSESSMENT OF TUMOR BURDEN</u>

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and

measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non–lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is $<$10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is $\geq$15 mm.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to $<$15 mm (or even $<$10 mm). However, if it subsequently decreases to $<$10 mm and all other lesions are no longer detectable or have also decreased to a short axis of $<$10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to $<$10 mm during the study. Thus, when lymph nodes are included in the sum of diameters,

the sum may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the

complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

Definitions of the criteria used to determine objective tumor response are provided below:

- Complete response (CR): Disappearance of all lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

  New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target or measurable new lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 1.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Can 2014;2:17

Appendix 5 Modified RECIST criteria for Malignant Pleural Mesothelioma

As previously described (Byrne and Nowak, 2004), RECIST 1.1 (Appendix 3) does not adequately describe the volume of pleural mesothelioma, and a modified RECIST system is a superior predictor of patient disease burden and outcome.

With the exception of measurement of pleural lesions, modified RECIST is identical to RECIST 1.1, as described in Appendix 3. Rather than reiterate the common elements of RECIST 1.1 and modified RECIST, we will focus here on the specific details of measuring pleural thickness using modified RECIST as described (Byrne and Nowak, 2004).

Tumor thickness perpendicular to the chest wall or mediastinum is measured in two positions at three separate levels on transverse cuts at least 1 cm apart and related to anatomical landmarks of CT scan. The sum of the six measurements defines a unidimensional pleural measure. Transverse cuts above the level of division of the main bronchi are preferred if at all possible.

At reassessment, pleural thickness is measured at the same position at the same level, ideally by the same observer.

Other measurable lesions are measured unidimensionally as per the RECIST criteria in Appendix 3. Unidimensional measurements are summed to obtain the total tumor measurement. Response criteria are identical to RECIST 1.1 (Appendix 3).

Appendix 6
Preexisting Autoimmune Diseases and Immune Deficiencies

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations

Appendix 8
Additional References

ALAKUS, H., BABICKY, M. L., GHOSH, P., YOST, S., JEPSEN, K., DAI, Y., ARIAS, A., SAMUELS, M. L., MOSE, E. S., SCHWAB, R. B., PETERSON, M. R., LOWY, A. M., FRAZER, K. A. & HARISMENDY, O. 2014. Genome-wide mutational landscape of mucinous carcinomatosis peritonei of appendiceal origin. *Genome Med,* 6**,** 43.

ASARE, E. A., COMPTON, C. C., HANNA, N. N., KOSINSKI, L. A., WASHINGTON, M. K., KAKAR, S., WEISER, M. R. & OVERMAN, M. J. 2016. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: Analysis of the National Cancer Data Base. *Cancer,* 122**,** 213-21.

BARBER, D. L., WHERRY, E. J., MASOPUST, D., ZHU, B., ALLISON, J. P., SHARPE, A. H., FREEMAN, G. J. & AHMED, R. 2006. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature,* 439**,** 682-7.

BENNOUNA, J., SASTRE, J., ARNOLD, D., OSTERLUND, P., GREIL, R., VAN CUTSEM, E., VON MOOS, R., VIEITEZ, J. M., BOUCHE, O., BORG, C., STEFFENS, C. C., ALONSO-ORDUNA, V., SCHLICHTING, C., REYES-RIVERA, I., BENDAHMANE, B., ANDRE, T., KUBICKA, S. & INVESTIGATORS, M. L. S. 2013. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol,* 14**,** 29-37.

BHATIA, S., AFANASIEV, O. & NGHIEM, P. 2011. Immunobiology of Merkel cell carcinoma: implications for immunotherapy of a polyomavirus-associated cancer. *Curr Oncol Rep,* 13**,** 488-97.

BLANK, C., GAJEWSKI, T. F. & MACKENSEN, A. 2005. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol Immunother,* 54**,** 307-14.

BRAHMER, J., RIZVI, N., LUTZKY, J., KHLEIF, S., BLAKE-HASKINS, A., LI, X., ROBBINS, P., VASSELLI, J., IBRAHIM, R. & ANTONIA, S. 2014. Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. *Journal of Clinical Oncology* 32**,** Abstract 8021

BRAHMER, J. R. 2013. Harnessing the immune system for the treatment of non-small-cell lung cancer. *J Clin Oncol,* 31**,** 1021-8.

BRAHMER, J. R., TYKODI, S. S., CHOW, L. Q., HWU, W. J., TOPALIAN, S. L., HWU, P., DRAKE, C. G., CAMACHO, L. H., KAUH, J., ODUNSI, K., PITOT, H. C., HAMID, O., BHATIA, S., MARTINS, R., EATON, K., CHEN, S., SALAY, T. M., ALAPARTHY, S., GROSSO, J. F., KORMAN, A. J., PARKER, S. M., AGRAWAL, S., GOLDBERG, S. M., PARDOLL, D. M., GUPTA, A. & WIGGINTON, J. M. 2012. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med,* 366**,** 2455-65.

BRUNNER, M., THURNHER, D., PAMMER, J., GELEFF, S., HEIDUSCHKA, G., REINISCH, C. M., PETZELBAUER, P. & EROVIC, B. M. 2008. Expression of VEGF-A/C, VEGF-R2, PDGF-alpha/beta, c-kit, EGFR, Her-2/Neu, Mcl-1 and Bmi-1 in Merkel cell carcinoma. *Mod Pathol,* 21**,** 876-84.

Appendix 8
Additional References (cont.)

BYRNE, M. J. & NOWAK, A. K. 2004. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol,* 15**,** 257-60.

CALABRO, L., MORRA, A., FONSATTI, E., CUTAIA, O., AMATO, G., GIANNARELLI, D., DI GIACOMO, A. M., DANIELLI, R., ALTOMONTE, M., MUTTI, L. & MAIO, M. 2013. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *Lancet Oncol,* 14**,** 1104-11.

CAPLIN, M. E., PAVEL, M., CWIKLA, J. B., PHAN, A. T., RADERER, M., SEDLACKOVA, E., CADIOT, G., WOLIN, E. M., CAPDEVILA, J., WALL, L., RINDI, G., LANGLEY, A., MARTINEZ, S., BLUMBERG, J., RUSZNIEWSKI, P. & INVESTIGATORS, C. 2014. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med,* 371**,** 224-33.

CARR, N. J., CECIL, T. D., MOHAMED, F., SOBIN, L. H., SUGARBAKER, P. H., GONZALEZ-MORENO, S., TAFLAMPAS, P., CHAPMAN, S. & MORAN, B. J. 2016. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol,* 40**,** 14-26.

CHEN, D. S., IRVING, B. A. & HODI, F. S. 2012. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res,* 18**,** 6580-7.

CHUA, D. T., SHAM, J. S. & AU, G. K. 2003. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol,* 39**,** 361-6.

DAVIES, M. 2014. New modalities of cancer treatment for NSCLC: focus on immunotherapy. *Cancer Manag Res,* 6**,** 63-75.

DAY, C. L., KAUFMANN, D. E., KIEPIELA, P., BROWN, J. A., MOODLEY, E. S., REDDY, S., MACKEY, E. W., MILLER, J. D., LESLIE, A. J., DEPIERRES, C., MNCUBE, Z., DURAISWAMY, J., ZHU, B., EICHBAUM, Q., ALTFELD, M., WHERRY, E. J., COOVADIA, H. M., GOULDER, P. J., KLENERMAN, P., AHMED, R., FREEMAN, G. J. & WALKER, B. D. 2006. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature,* 443**,** 350-4.

FANG, W., ZHANG, J., HONG, S., ZHAN, J., CHEN, N., QIN, T., TANG, Y., ZHANG, Y., KANG, S., ZHOU, T., WU, X., LIANG, W., HU, Z., MA, Y., ZHAO, Y., TIAN, Y., YANG, Y., XUE, C., YAN, Y., HOU, X., HUANG, P., HUANG, Y., ZHAO, H. & ZHANG, L. 2014. EBV-driven LMP1 and IFN-gamma up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. *Oncotarget,* 5**,** 12189-202.

FEHRENBACHER, L., SPIRA, A., BALLINGER, M., KOWANETZ, M., VANSTEENKISTE, J., MAZIERES, J., PARK, K., SMITH, D., ARTAL-CORTES, A., LEWANSKI, C., BRAITEH, F., WATERKAMP, D., HE, P., ZOU, W., CHEN, D. S., YI, J., SANDLER, A., RITTMEYER, A. & GROUP, P. S. 2016. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet,* 387**,** 1837-46.

FENG, H., SHUDA, M., CHANG, Y. & MOORE, P. S. 2008. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science,* 319**,** 1096-100.

Appendix 8
Additional References (cont.)

FOO, K. F., TAN, E. H., LEONG, S. S., WEE, J. T., TAN, T., FONG, K. W., KOH, L., TAI, B. C., LIAN, L. G. & MACHIN, D. 2002. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol,* 13**,** 150-6.

FORMAN, D., DE MARTEL, C., LACEY, C. J., SOERJOMATARAM, I., LORTET-TIEULENT, J., BRUNI, L., VIGNAT, J., FERLAY, J., BRAY, F., PLUMMER, M. & FRANCESCHI, S. 2012. Global burden of human papillomavirus and related diseases. *Vaccine,* 30 Suppl 5**,** F12-23.

HODI, F. S., LAWRENCE, D., LEZCANO, C., WU, X., ZHOU, J., SASADA, T., ZENG, W., GIOBBIE-HURDER, A., ATKINS, M. B., IBRAHIM, N., FRIEDLANDER, P., FLAHERTY, K. T., MURPHY, G. F., RODIG, S., VELAZQUEZ, E. F., MIHM, M. C., JR., RUSSELL, S., DIPIRO, P. J., YAP, J. T., RAMAIYA, N., VAN DEN ABBEELE, A. D., GARGANO, M. & MCDERMOTT, D. 2014. Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res,* 2**,** 632-42.

HODI, F. S., O'DAY, S. J., MCDERMOTT, D. F., WEBER, R. W., SOSMAN, J. A., HAANEN, J. B., GONZALEZ, R., ROBERT, C., SCHADENDORF, D., HASSEL, J. C., AKERLEY, W., VAN DEN EERTWEGH, A. J., LUTZKY, J., LORIGAN, P., VAUBEL, J. M., LINETTE, G. P., HOGG, D., OTTENSMEIER, C. H., LEBBE, C., PESCHEL, C., QUIRT, I., CLARK, J. I., WOLCHOK, J. D., WEBER, J. S., TIAN, J., YELLIN, M. J., NICHOL, G. M., HOOS, A. & URBA, W. J. 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med,* 363**,** 711-23.

JANNE, P. A., WOZNIAK, A. J., BELANI, C. P., KEOHAN, M. L., ROSS, H. J., POLIKOFF, J. A., MINTZER, D. M., TAYLOR, L., ASHLAND, J., YE, Z., MONBERG, M. J. & OBASAJU, C. K. 2005. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. *Clin Lung Cancer,* 7**,** 40-6.

KANTOFF, P. W., HIGANO, C. S., SHORE, N. D., BERGER, E. R., SMALL, E. J., PENSON, D. F., REDFERN, C. H., FERRARI, A. C., DREICER, R., SIMS, R. B., XU, Y., FROHLICH, M. W., SCHELLHAMMER, P. F. & INVESTIGATORS, I. S. 2010. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med,* 363**,** 411-22.

KARIM, S. & LEIGHL, N. 2016. Pembrolizumab for the treatment of thoracic malignancies: current landscape and future directions. *Future Oncol,* 12**,** 9-23.

KEIR, M. E., BUTTE, M. J., FREEMAN, G. J. & SHARPE, A. H. 2008. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol,* 26**,** 677-704.

KOUVARAKI, M. A., AJANI, J. A., HOFF, P., WOLFF, R., EVANS, D. B., LOZANO, R. & YAO, J. C. 2004. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 22**,** 4762-71.

KRISHNA, S. M., JAMES, S. & BALARAM, P. 2006. Expression of VEGF as prognosticator in primary nasopharyngeal cancer and its relation to EBV status. *Virus Res,* 115**,** 85-90.

KUKKO, H., KOLJONEN, V., LASSUS, P., TUKIAINEN, E., HAGLUND, C. & BOHLING, T. 2007. Expression of vascular endothelial growth factor receptor-2 in Merkel cell carcinoma. *Anticancer Res,* 27**,** 2587-9.

Appendix 8
Additional References (cont.)

LEE, N. Y., ZHANG, Q., PFISTER, D. G., KIM, J., GARDEN, A. S., MECHALAKOS, J., HU, K., LE, Q. T., COLEVAS, A. D., GLISSON, B. S., CHAN, A. T. & ANG, K. K. 2012. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. *Lancet Oncol,* 13**,** 172-80.

LEMOS, B. D., STORER, B. E., IYER, J. G., PHILLIPS, J. L., BICHAKJIAN, C. K., FANG, L. C., JOHNSON, T. M., LIEGEOIS-KWON, N. J., OTLEY, C. C., PAULSON, K. G., ROSS, M. I., YU, S. S., ZEITOUNI, N. C., BYRD, D. R., SONDAK, V. K., GERSHENWALD, J. E., SOBER, A. J. & NGHIEM, P. 2010. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol,* 63**,** 751-61.

LIPSON, E. J., VINCENT, J. G., LOYO, M., KAGOHARA, L. T., LUBER, B. S., WANG, H., XU, H., NAYAR, S. K., WANG, T. S., SIDRANSKY, D., ANDERS, R. A., TOPALIAN, S. L. & TAUBE, J. M. 2013. PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. *Cancer Immunol Res,* 1**,** 54-63.

MANSFIELD, A., PEIKERT, T., RODEN, A., KRCO, C., HARRINGTON, S., DONG, H. & KWON, E. 2014. Programmed cell death 1 ligand 1 expression and association with survival in mesothelioma. *Journal of Thoracic Oncology,* 9 S7-S52.

MANZONI, M., ROVATI, B., RONZONI, M., LOUPAKIS, F., MARIUCCI, S., RICCI, V., GATTONI, E., SALVATORE, L., TINELLI, C., VILLA, E. & DANOVA, M. 2010. Immunological effects of bevacizumab-based treatment in metastatic colorectal cancer. *Oncology,* 79**,** 187-96.

MCCUSKER, M. E., COTE, T. R., CLEGG, L. X. & SOBIN, L. H. 2002. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer,* 94**,** 3307-12.

MOERTEL, C. G., HANLEY, J. A. & JOHNSON, L. A. 1980. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *The New England journal of medicine,* 303**,** 1189-94.

MOERTEL, C. G., LEFKOPOULO, M., LIPSITZ, S., HAHN, R. G. & KLAASSEN, D. 1992. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *The New England journal of medicine,* 326**,** 519-23.

NGEOW, J., LIM, W. T., LEONG, S. S., ANG, M. K., TOH, C. K., GAO, F., CHOWBAY, B. & TAN, E. H. 2011. Docetaxel is effective in heavily pretreated patients with disseminated nasopharyngeal carcinoma. *Ann Oncol,* 22**,** 718-22.

NGHIEM, P. T., BHATIA, S., LIPSON, E. J., KUDCHADKAR, R. R., MILLER, N. J., ANNAMALAI, L., BERRY, S., CHARTASH, E. K., DAUD, A., FLING, S. P., FRIEDLANDER, P. A., KLUGER, H. M., KOHRT, H. E., LUNDGREN, L., MARGOLIN, K., MITCHELL, A., OLENCKI, T., PARDOLL, D. M., REDDY, S. A., SHANTHA, E. M., SHARFMAN, W. H., SHARON, E., SHEMANSKI, L. R., SHINOHARA, M. M., SUNSHINE, J. C., TAUBE, J. M., THOMPSON, J. A., TOWNSON, S. M., YEARLEY, J. H., TOPALIAN, S. L. & CHEEVER, M. A. 2016. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med,* 374**,** 2542-52.

Appendix 8
Additional References (cont.)

OXNARD, G. R., WILCOX, K. H., GONEN, M., POLOTSKY, M., HIRSCH, B. R. & SCHWARTZ, L. H. 2016. Response Rate as a Regulatory End Point in Single-Arm Studies of Advanced Solid Tumors. *JAMA Oncol,* 2**,** 772-9.

QIAN, C. N., ZHANG, C. Q., GUO, X., HONG, M. H., CAO, S. M., MAI, W. Y., MIN, H. Q. & ZENG, Y. X. 2000. Elevation of serum vascular endothelial growth factor in male patients with metastatic nasopharyngeal carcinoma. *Cancer,* 88**,** 255-61.

RAGHAV, K. P., SHETTY, A. V., KAZMI, S. M., ZHANG, N., MORRIS, J., TAGGART, M., FOURNIER, K., ROYAL, R., MANSFIELD, P., ENG, C., WOLFF, R. A. & OVERMAN, M. J. 2013. Impact of molecular alterations and targeted therapy in appendiceal adenocarcinomas. *Oncologist,* 18**,** 1270-7.

RAYMOND, E., DAHAN, L., RAOUL, J.-L., BANG, Y.-J., BORBATH, I., LOMBARD-BOHAS, C., VALLE, J., METRAKOS, P., SMITH, D., VINIK, A., CHEN, J.-S., HÖRSCH, D., HAMMEL, P., WIEDENMANN, B., VAN CUTSEM, E., PATYNA, S., LU, D. R., BLANCKMEISTER, C., CHAO, R. & RUSZNIEWSKI, P. 2011. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *The New England journal of medicine,* 364**,** 501-13.

RINKE, A., MULLER, H. H., SCHADE-BRITTINGER, C., KLOSE, K. J., BARTH, P., WIED, M., MAYER, C., AMINOSSADATI, B., PAPE, U. F., BLAKER, M., HARDER, J., ARNOLD, C., GRESS, T., ARNOLD, R. & GROUP, P. S. 2009. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol,* 27**,** 4656-63.

RODRIGUEZ, D., CHEUNG, M. C., HOUSRI, N. & KONIARIS, L. G. 2009. Malignant abdominal mesothelioma: defining the role of surgery. *J Surg Oncol,* 99**,** 51-7.

ROLLISON, D. E., GIULIANO, A. R. & BECKER, J. C. 2010. New virus associated with merkel cell carcinoma development. *J Natl Compr Canc Netw,* 8**,** 874-80.

ROSENBERG, J. E., HOFFMAN-CENSITS, J., POWLES, T., VAN DER HEIJDEN, M. S., BALAR, A. V., NECCHI, A., DAWSON, N., O'DONNELL, P. H., BALMANOUKIAN, A., LORIOT, Y., SRINIVAS, S., RETZ, M. M., GRIVAS, P., JOSEPH, R. W., GALSKY, M. D., FLEMING, M. T., PETRYLAK, D. P., PEREZ-GRACIA, J. L., BURRIS, H. A., CASTELLANO, D., CANIL, C., BELLMUNT, J., BAJORIN, D., NICKLES, D., BOURGON, R., FRAMPTON, G. M., CUI, N., MARIATHASAN, S., ABIDOYE, O., FINE, G. D. & DREICER, R. 2016. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet,* 387**,** 1909-20.

SMEENK, R. M., VERWAAL, V. J., ANTONINI, N. & ZOETMULDER, F. A. 2007. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg,* 245**,** 104-9.

STEBBING, J., POWLES, T., MCPHERSON, K., SHAMASH, J., WELLS, P., SHEAFF, M. T., SLATER, S., RUDD, R. M., FENNELL, D. & STEELE, J. P. 2009. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer,* 63**,** 94-7.

THOMAS, A. & HASSAN, R. 2012. Immunotherapies for non-small-cell lung cancer and mesothelioma. *Lancet Oncol,* 13**,** e301-10.

TSAO, A. S., WISTUBA, I., ROTH, J. A. & KINDLER, H. L. 2009. Malignant pleural mesothelioma. *J Clin Oncol,* 27**,** 2081-90.

Appendix 8
Additional References (cont.)

VAN MEERBEECK, J. P., BAAS, P., DEBRUYNE, C., GROEN, H. J., MANEGOLD, C., ARDIZZONI, A., GRIDELLI, C., VAN MARCK, E. A., LENTZ, M. & GIACCONE, G. 1999. A Phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *Cancer,* 85**,** 2577-82.

VOGELZANG, N. J., RUSTHOVEN, J. J., SYMANOWSKI, J., DENHAM, C., KAUKEL, E., RUFFIE, P., GATZEMEIER, U., BOYER, M., EMRI, S., MANEGOLD, C., NIYIKIZA, C. & PAOLETTI, P. 2003. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol,* 21**,** 2636-44.

YAO, J. C., HASSAN, M., PHAN, A., DAGOHOY, C., LEARY, C., MARES, J. E., ABDALLA, E. K., FLEMING, J. B., VAUTHEY, J.-N., RASHID, A. & EVANS, D. B. 2008. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 26**,** 3063-72.

YAO, J. C., LOMBARD-BOHAS, C., BAUDIN, E., KVOLS, L. K., ROUGIER, P., RUSZNIEWSKI, P., HOOSEN, S., ST PETER, J., HAAS, T., LEBWOHL, D., VAN CUTSEM, E., KULKE, M. H., HOBDAY, T. J., O'DORISIO, T. M., SHAH, M. H., CADIOT, G., LUPPI, G., POSEY, J. A. & WIEDENMANN, B. 2010. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* 28**,** 69-76.

ZALCMAN, G., MAZIERES, J., MARGERY, J., GREILLIER, L., AUDIGIER-VALETTE, C., MORO-SIBILOT, D., MOLINIER, O., CORRE, R., MONNET, I., GOUNANT, V., RIVIERE, F., JANICOT, H., GERVAIS, R., LOCHER, C., MILLERON, B., TRAN, Q., LEBITASY, M. P., MORIN, F., CREVEUIL, C., PARIENTI, J. J., SCHERPEREEL, A. & FRENCH COOPERATIVE THORACIC, I. 2015. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*.

ZALCMAN, G., MAZIERES, J., MARGERY, J., GREILLIER, L., AUDIGIER-VALETTE, C., MORO-SIBILOT, D., MOLINIER, O., CORRE, R., MONNET, I., GOUNANT, V., RIVIERE, F., JANICOT, H., GERVAIS, R., LOCHER, C., MILLERON, B., TRAN, Q., LEBITASY, M. P., MORIN, F., CREVEUIL, C., PARIENTI, J. J., SCHERPEREEL, A. & FRENCH COOPERATIVE THORACIC, I. 2016. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet,* 387**,** 1405-14.