Supplementary Data

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

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1. Supplementary methods 1

Following methodology was used for collecting and analyzing the real-world evidence for treatment of patients with malignant peritoneal mesothelioma (MPeM) off-current trial for comparison with outcomes on the current trial of atezolizumab and bevacizumab (AtezoBev) in MPeM:

Clinical course of trial patients on pre-study platinum-pemetrexed chemotherapy (N = 20)

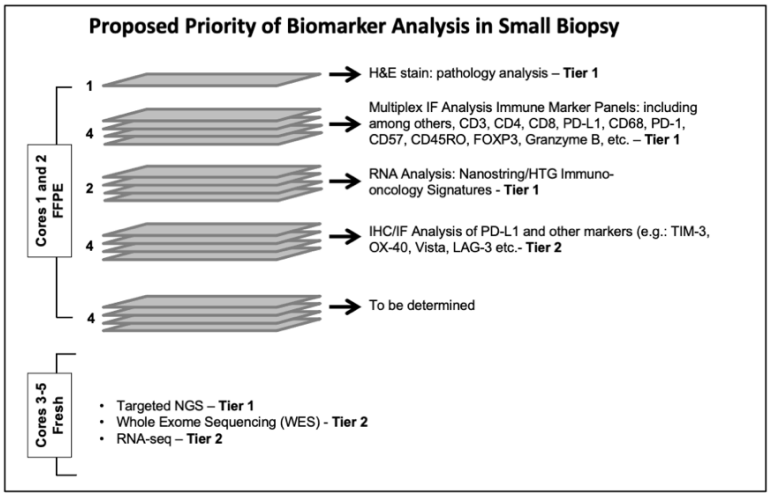
To address any concerns of selection bias pertaining to indolent tumor biology of trial patients that may confound objective response rate (ORR) and progression-free survival (PFS), we evaluated patient and population dynamics of the study cohort prior to study enrollment. We looked at the pre-enrollment treatment data on patients with MPeM who were enrolled on the current study and received AtezoBev. Since platinum-pemetrexed is the standard of care for patients with MPeM and prior treatment was an eligibility criterion for study enrollment, all 20 patients received this chemotherapy. Data on treatment course on platinum-pemetrexed chemotherapy prior to study enrollment was collected using electronic medical records (source data). Tumor response was categorized as either disease regression, stability or progression as per radiology report and treating physician assessment. Time to next treatment was defined as the time interval between date of treatment initiation and date of commencement of next line of therapy as per treating physician discretion (progression of disease – 17 [85%] and poor tolerability – 3 [15%]). In case of use of maintenance pemetrexed after initial platinum-pemetrexed course, the duration of pemetrexed as well as reintroduction of platinum was included in this interval including duration of treatment breaks. We compared this time to next treatment on standard of care first-line platinum-pemetrexed chemotherapy for all 20 study patients prior to enrollment to AtezoBev to their duration of treatment on AtezoBev on trial.

2. Supplementary methods 2

A. Sample collection and processing

Fresh core needle biopsies (CNBs) or excisional biopsies were obtained with the purpose of research studies before and after treatment (Cycle 2 Day 1) and sent to the MD Anderson Institutional Tissue Bank (ITB) immediately after collection. At least 5 tissue cores were attempted from the CNB/surgical procedure based on patient's clinical condition at the time of biopsy and determined by the radiologist performing the procedure. These cores/surgical excision pieces were processed as follows.

Figure A1. Prioritization of biomarker analyses



B. Histology evaluation and quality control

Hematoxylin and Eosin (H&E) stained sections from CNBs and surgical excisions were used to confirm the presence of tumor cells, as well as their abundance (tumor cellularity), stromal components and lymphocytic infiltrates. H&E-stained sections from all FFPE diagnostic slides (tumor, normal and lymph nodes) were scanned in Aperio™ digital pathology scanner analysis for pathological evaluation and selection of 1 or 2 blocks (depending on tumor availability) for biomarker analysis. All tissue specimens collected were reviewed by reference pathologists at a central laboratory. At least, three types of QC activities for specimens collected were performed: a) histology/cytology examination of the tissues and cells, b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence and c) quality assessment of DNA, RNA and protein extracted. Blood (plasma and PMBCs), tumor (CNB and surgical excision specimens) samples will be subjected to DNA, RNA and protein extraction using standard methods. DNA and RNA quantity and integrity was assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses.

C. *Immunohistochemistry (IHC) analyses*

IHC stains for microsatellite instability (MSI) status were done with specific antibody staining of treated formalin-fixed, paraffin embedded (FFPE) tissue samples. Briefly, 5-µm sections were baked in oven for 30 minutes and loaded into the Leica Bond III automated system (Leica Microsystems, Buffalo Grove, Illinois), as per manufacturer's protocol. Samples were challenged with specific antibodies to the proteins of interest (Table A1). Prior to secondary antibody challenge blocking, the samples were bathed in blocking serum. Secondary biotin-conjugated antibodies were then added. The stain was visualized using 3,3′-diaminobenzidine and hematoxylin counterstain. Appropriate positive-negative controls were performed simultaneously. Staining was evaluated by pathologists with expertise in IHC and MSI assessment who were blinded to clinical data. Results were reported as either MSI-Low (MSS) if there was intact nuclear expression evident for all four proteins in carcinoma cells or MSI-High (MSI-H) if expression was lost in any of the proteins in the carcinoma cells.

IHC stain for PD-L1 status was done using specific antibody staining of FFPE tissue samples (Table C1). Briefly, 4-µm sections were baked in the oven for 12 minutes and loaded into Leica Bond Max autostainer (Leica Biosystems, Vista, CA), as per manufacturer's protocol. Samples were then challenged with specific antibodies to the proteins of interest (Table A1). The stain was visualized using hematoxylin II counterstain. Appropriate positive-negative controls were performed simultaneously. Staining was evaluated by pathologists with expertise in IHC and PD-L1 assessment and blinded to clinical data. Staining was reported as proportion of tumor cells with PD-L1 staining (discernible membrane staining of any intensity), estimated as the percentage of PD-L1 positive tumor cells over the total tumor cells.

Table C1. List of antibodies for MSI and PD-L1

Antibody	Clone	Dilution	Epitope Retrieval	Source
MLH1	G168-728	1:300	Tris–EDTA Buffer, 10 min	Cell Marque, Rocklin, CA, USA
MSH2	FE11	1:100	Tris–EDTA Buffer, 20 min	Calbiochem, San Diego, CA, USA
MSH6	44	1:300	Citrate Buffer, 20 min	BD Biosciences, San Diego, CA, USA
PMS2	A16-4	1:125	Tris–EDTA Buffer, 20 min	BD Biosciences, San Diego, CA, USA
PD-L1	SP263	1:75	Tris-HCl with 1% carrier protein	Ventana Medical Systems Inc, Tucson, AZ, USA

D. *Whole-exome sequencing (WES) data processing*

Raw output of the Illumina exome sequencing data was processed using Illumina's Consensus Assessment of Sequence And Variation (CASAVA) tool (v1.8.2) (http://support.illumina.com/sequencing/sequencing_software/casava.html) for demultiplexing and conversion to FASTQ format. The FASTQ files were aligned to the human reference genome (hg19) using BWA (v0.7.5) allowing up to 3 mismatches (2 mismatches must be in the first 40 seed regions) for a 76-base sequencing run.(1) The aligned BAM files were then subjected to mark duplication, realignment and base recalibration using Picard (v1.112) and GATK (v3.3.1) software tools.(2) The generated BAM files were then used for downstream analysis. Genotyping quality check was performed to rule out any possible sample swapping or contamination. Briefly, germline SNPs were called using Platypus (v0.5.2).(3) Samples from the same patient were confirmed/identified by percentage of genotyping-identity between them, which was

defined by the fraction of identical germline alleles among the overlapping SNPs between the two samples. All samples in this study passed quality check. No sample swapping or contamination was detected.

E. Somatic mutation calling and filtering

MuTect (v1.1.4) was applied to identify somatic point mutations and Pindel (v0.2.4) was applied to identify small insertion and deletions (Indels).(4,5) The MuTect and Pindel outputs were then processed using the Cancer Genomics Lab (MD Anderson Cancer Center) for filtering and annotation. Briefly, only MuTect calls marked as "KEEP" were selected and taken into the next step. For both substitutions and Indels, mutations with a low variant allelic fraction (VAF < 0.02) or had a low total read coverage (< 20 reads for tumor samples; <10 reads for matching normal sample), were removed. In addition, Indels that had an immediate repeat region within 25 base pairs downstream towards its 3' region were also removed. Common variants reported by the ExAc (the Exome Aggregation Consortium, http://exac.broadinstitute.org), Phase-3 1000 Genome Project (http://phase3browser.1000genomes.org/Homo_sapiens/Info/Index), or the NHLBI GO Exome Sequencing Project (ESP6500, http://evs.gs.washington.edu/EVS/) with a population minor allele frequency greater than 1% were removed. For the tumor mutational burden (TMB) calculation, only variants with an annotation of "Frame_Shift_Del", "Frame_Shift_Ins", "In_Frame_Del", "In_Frame_Ins", "Missense_Mutation", "Nonsense_Mutation ", "Silent", "Splice_Site", "Translation_Start_Site" and "Nonstop_Mutation" were kept for the analysis.

F. RNA sequencing and data analysis

FASTQ files of RNA samples are processed using both STAR aligner (v2.6.0) following the two-step alignment procedure and TopHat (v2.1.0) and Cufflinks (v2.2.1).(6-8) Read counts were obtained using HTSeq (v0.11.0).(9) Transcripts without read counts were removed before normalization and differential expression analysis performed using R package DESeq2 (v1.28.1).(10) Expression levels were considered significantly different between two groups when genes with log2 fold change greater than 1 and q value (false discovery rate or FDR) < 0.05. Normalized counts were transformed using the variance-stabilizing transformation (VST) module in DESeq2 for downstream analyses. The heatmaps were generated using R package pheatmap (v1.0.12) on VST-transformed counts. Of note, only 2 of the 20 patients had biopsies from extra-peritoneal sites (abdominal wall lesions). Due to the limited number of these patients, gene differential analysis performed on RNA sequencing data did not take into account the site of biopsy (peritoneal vs. extraperitoneal).

G. Gene signature score

Normalized gene signature enrichment scores were calculated using in R package GSVA (v1.36.1) with default parameters.(11) Gene signatures score with association to following disease biology were calculated as per Table G1.

Table G1. List of gene expression signatures scores used for correlative analyses

Score	**McDermott et al.(12) Nature medicine, 2018**	**Franzini et al.(13) Clinical Cancer Research 2020**	**Thompson et al.(14) Lung cancer, 2020**

Tumor Biology	Immune-Sensitivity		Angiogenesis	Epithelial Mesenchymal Transition	
Genes	*CD8A*	*CD274*	*VEGFA*	*CDH1*	*MMP2*
	CD27	*CTLA4*	*KDR*	*CDH3*	*AGER*
	IFNG	*FOXP3*	*ESM1*	*CLDN4*	
	GZMA	*TIGIT*	*PECAM1*	*EPCAM*	
	GZMB	*IDO1*	*ANGPTL4*	*ST14*	
	PRF1	*PSMB8*	*CD34*	*MAL2*	
	EOMES	*PSMB9*		*VIM*	
	CXCL9	*TAP1*		*SNAI2*	
	CXCL10	*TAP2*		*ZEB2*	
	CXCL11			*FN1*	

H. Vectra Analysis

Analysis of FFPE samples was done using an antibody panel to characterize the expression of cancer cells and subsets of tumor associated immune cells: pancytokeratin (AE1/AE3), CK7, DAPI and 7 immune markers distributed in 2 panels PD-1, PD-L1, CD3, CD8, CD68, FOXP3 and CD45RO. For multiplex immunofluorescence (IF) analysis, we used the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software. Analysis was performed using the InForm software. The expression of protein markers and inflammatory cells was examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. Simultaneous marker expression was quantified using the Vectra 3.0™ multispectral microscopy and image analysis InForm™ 2.2.1 software (PerkinElmer). Mutually exclusive combinations of markers on a per cell basis were created from the InForm cell segmentation files. Normalized counts, nearest neighbor relationships, and concentrations of markers on a bivariate basis were analyzed and visualized using the Foundry (Syntropy) platform.

I. Clinical methods

- Eligible patients were ≥18 years old, had histologically confirmed advanced MPeM not amenable to definitive CRS (according to peritoneal-multidisciplinary tumor board) and had received at least one line of systemic chemotherapy involving platinum-pemetrexed doublet. Patient were required to have either progression on prior platinum-pemetrexed chemotherapy or adverse-events that precluded treatment (hypersensitivity to platinum, poor patient tolerance, worsening renal functions despite dose adjustment). Patients were required to have measurable disease according to Response Evaluation Criteria in Solid Tumors-version1.1 (RECISTv1.1), an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and normal organ/bone marrow function. Extraperitoneal metastases including pleural and lung metastases were allowed. Full eligibility criteria are provided in study protocol (Supplementary-Protocol).

- All pathological diagnosis of mesothelioma was confirmed at MD Anderson by reference pathologists with high level of expertise in diagnosis of pleural and peritoneal mesotheliomas.
- History of prior asbestos exposure was ascertained using patient reported occupational/exposure history assessment by treating provider documented in electronic medical records.
- Prior bevacizumab was allowed. The rationale for this was that although first-line anti-PD1 is not a standard of care for patients with peritoneal mesothelioma, bevacizumab may sometimes be used with chemotherapy based on the results of MAPS study in pleural mesothelioma.(15) However this is not a universal practice since no patients with peritoneal mesothelioma were included in the MAPS study. Since the rationale for the study was based on the ability of bevacizumab to modulate (ameliorate) a VEGF induced immunosuppressive tumor microenvironment, it was not felt that prior bevacizumab would alter response to the combination adversely. On the other hand, escape mechanisms to prior immunotherapies (IOs) may be related to mechanisms, not targeted by the combination.
- Key exclusion criteria were any prior immunotherapy, diagnosis of active autoimmune disease or immunodeficiency, concurrent malignancy, any known history of active/untreated central nervous system metastases and ongoing systemic immunosuppressive therapy at time of enrollment.

J. Study oversight

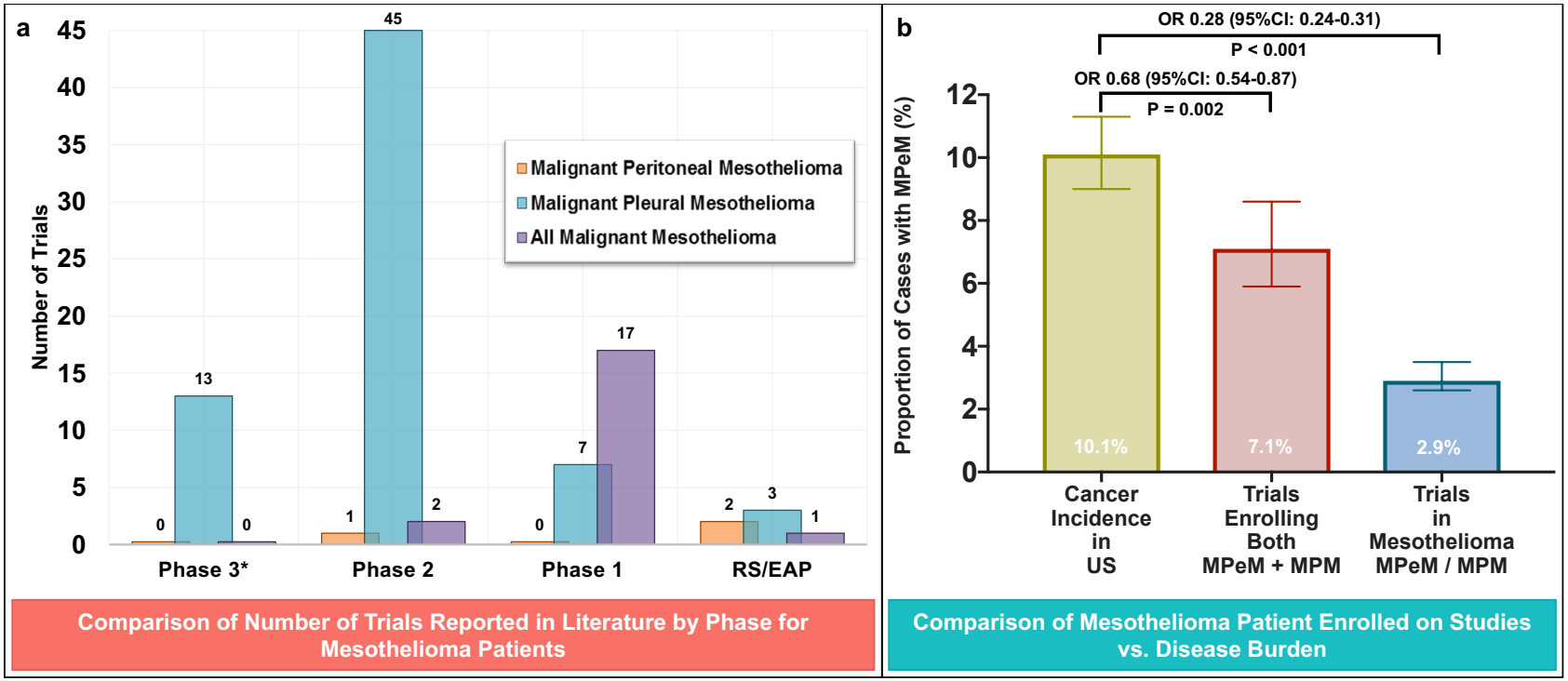
The principal investigators, in collaboration with a Joint Steering Committee (JSC) (comprising of members from MD Anderson Cancer Center and F. Hoffmann–La Roche/Genentech), developed the protocol and were responsible for study oversight. The protocol and all amendments were approved by the University of Texas M.D. Anderson Institutional Review Board (IRB). The study was conducted in accordance with Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Patients provided written informed consent before study enrollment. All authors were involved in data analysis and manuscript preparation and vouch for the integrity and completeness of the data reported and adherence to study protocol. Study is registered in ClinicalTrials.gov (NCT03074513). Full protocol is provided (Supplementary-Protocol).

K. Data sharing

Study protocol and statistical analysis plan are provided as supplementary material to the manuscript. Other de-identified participant data and applicable supporting clinical trial documents (including data dictionary) may be available upon reasonable request. All information requests should be sent to the corresponding author, Dr. Kanwal Raghav (kpraghav@mdanderson.org). Where clinical trial data are provided, MD Anderson Cancer Center will protect the privacy of our clinical trial participants.

3. Figure S1. Comparison of prospective trials in malignant peritoneal (MPeM) and pleural mesothelioma (MPM).

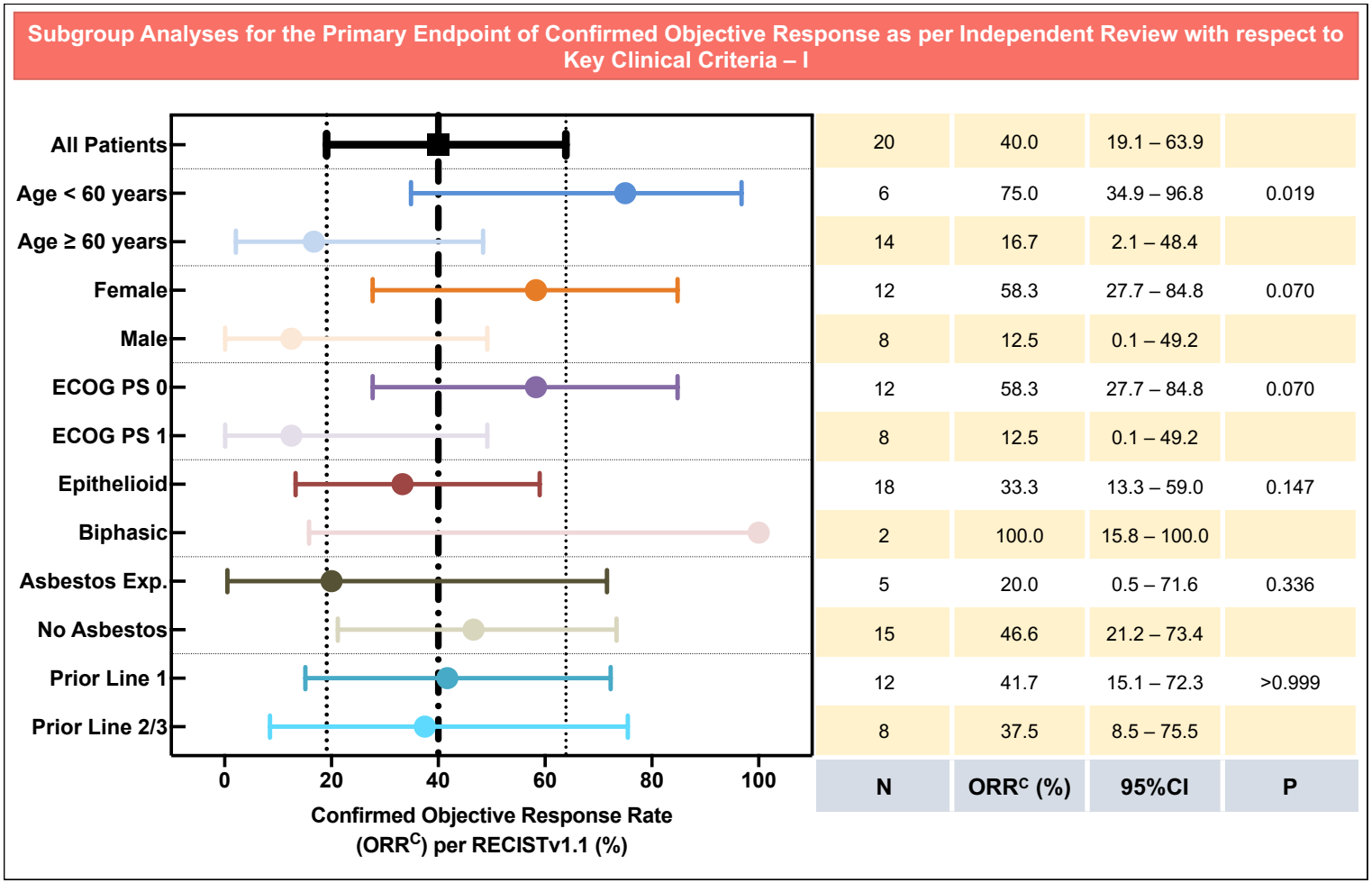
We systematically reviewed published prospective clinical trials for malignant mesothelioma (MM) between Oct 2002 (when the New Drug Application for pemetrexed, the only approved drug for mesothelioma, was submitted to U.S. Food and Drug Administration) and Nov 2019 (when first analysis of data on current study was performed), using PubMed.(16) Search terms included "Peritoneal Mesothelioma", "Pleural Mesothelioma" or "Mesothelioma" [Title]. Searched studies were reviewed and those involving systemic therapy for metastatic disease were included. Trials involving surgery, neoadjuvant or adjuvant chemotherapy were excluded. Study characteristics and patient distribution with regards to MPeM and MPM were obtained from original reports. Studies were classified as those done exclusively for MPeM, MPM and those that allowed both mesothelioma (MM) patients. The 95% confidence interval (95%CI) was calculated using Clopper and Pearson method. Proportions of patients on trials was compared to proportion of annual MPeM vs. MPM incidence in the United States (US) using Fisher's-exact test.(17) **Compared to MPM, MPeM had very few published trials (Panel a). Likewise, the proportion of MPeM patients enrolled on all trials and trials that allowed both MM patients was significantly lower than the burden of disease arguing for dedicated trials in this space (Panel b).**



Abbreviations: *RS/EAP, registry study/expanded access program; OR, odds ratio*

4. Figure S2. Antitumor activity by key clinicopathological subgroups of malignant peritoneal mesothelioma (MPeM).

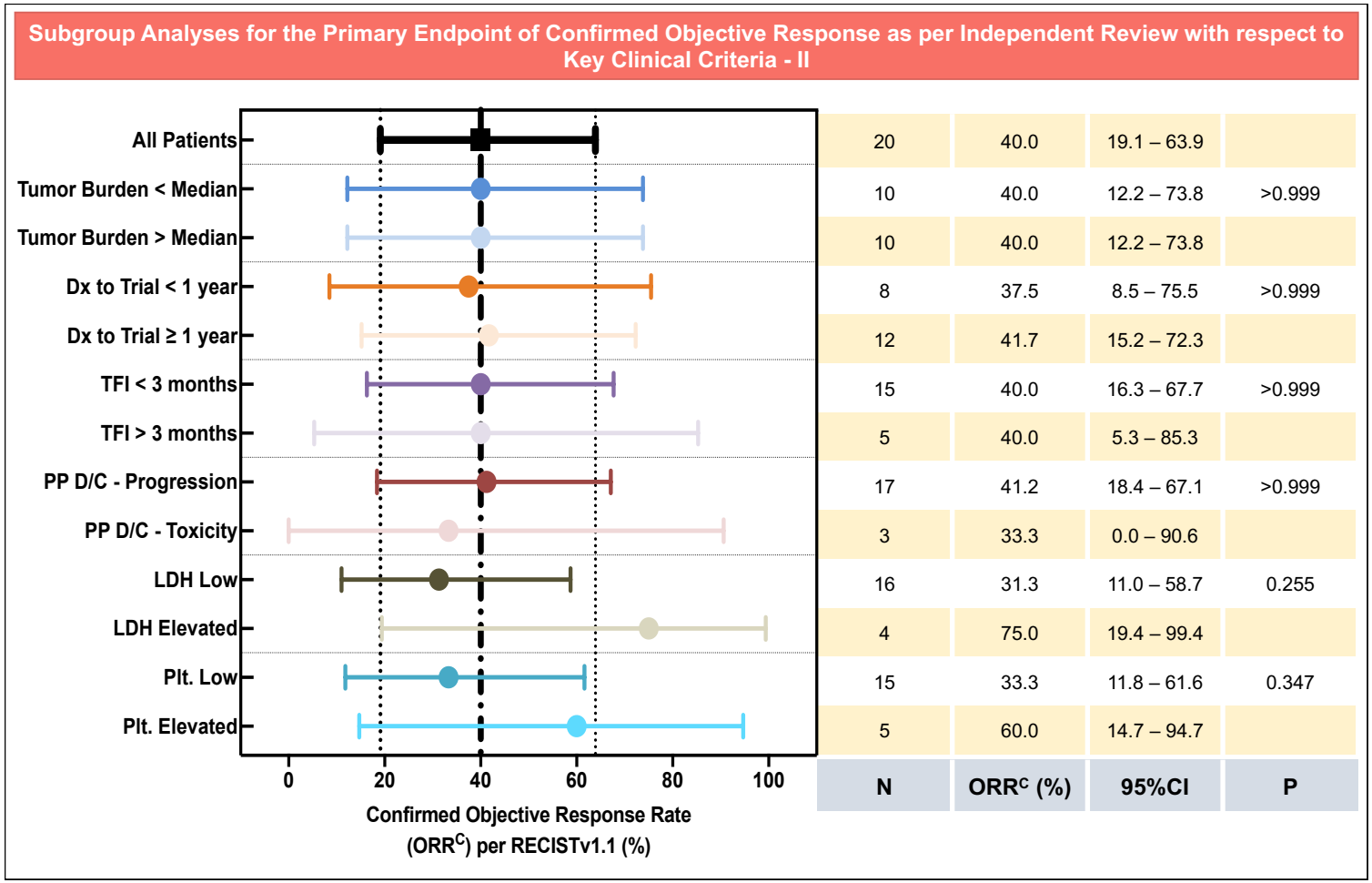
Forest-plot of post-hoc sub-group analysis of confirmed objective response rate (ORR^C) defined as proportion of patients who had Response Evaluation Criteria in Solid Tumors - version 1.1 partial response (PR) based on key characteristics with clinical impact in patients with MPeM. **Similar efficacy was seen in all subgroups.** Responses were seen more frequently in younger patients, women and those with Eastern Cooperative Oncology Group – performance status (ECOG PS) 0.



Abbreviations: *95%CI, 95% confidence interval; Exp., exposure*

5. Figure S2 (cont.). Antitumor activity by key clinicopathological subgroups of malignant peritoneal mesothelioma (MPeM).

Forest-plot of post-hoc sub-group analysis of confirmed objective response rate (ORR^C) defined as proportion of patients who had Response Evaluation Criteria in Solid Tumors - version 1.1 partial response (PR) based on key characteristics with clinical impact in patients with MPeM. **Similar efficacy was seen in all subgroups.** Tumor burden was measured using sum of target lesions as per RECIST v1.1.

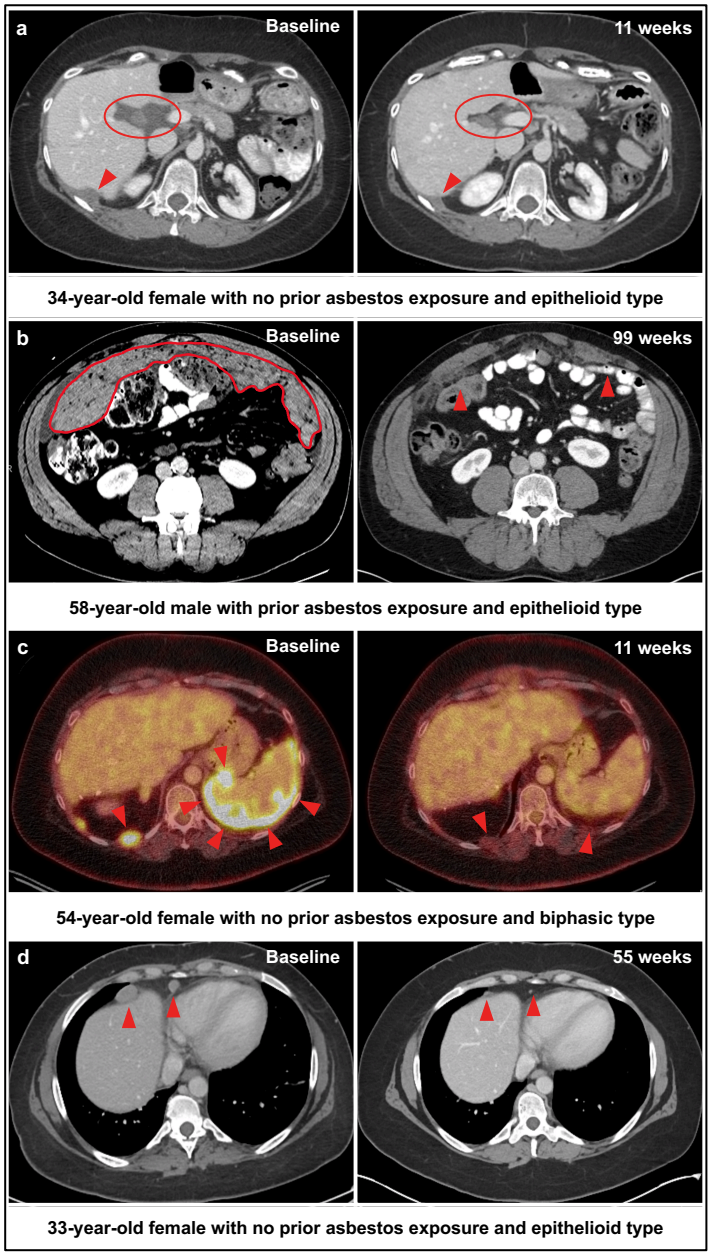


	N	ORR^C (%)	95%CI	P
All Patients	20	40.0	19.1 – 63.9	
Tumor Burden < Median	10	40.0	12.2 – 73.8	>0.999
Tumor Burden > Median	10	40.0	12.2 – 73.8	
Dx to Trial < 1 year	8	37.5	8.5 – 75.5	>0.999
Dx to Trial ≥ 1 year	12	41.7	15.2 – 72.3	
TFI < 3 months	15	40.0	16.3 – 67.7	>0.999
TFI > 3 months	5	40.0	5.3 – 85.3	
PP D/C - Progression	17	41.2	18.4 – 67.1	>0.999
PP D/C - Toxicity	3	33.3	0.0 – 90.6	
LDH Low	16	31.3	11.0 – 58.7	0.255
LDH Elevated	4	75.0	19.4 – 99.4	
Plt. Low	15	33.3	11.8 – 61.6	0.347
Plt. Elevated	5	60.0	14.7 – 94.7	

Abbreviations: *95%CI, 95% confidence interval; Dx, diagnosis; LDH, lactate dehydrogenase; Plt., platelet; PP D/C; reason for discontinuation of prior platinum-pemetrexed chemotherapy TFI, treatment free interval (interval between last chemotherapy and start of trial therapy)*

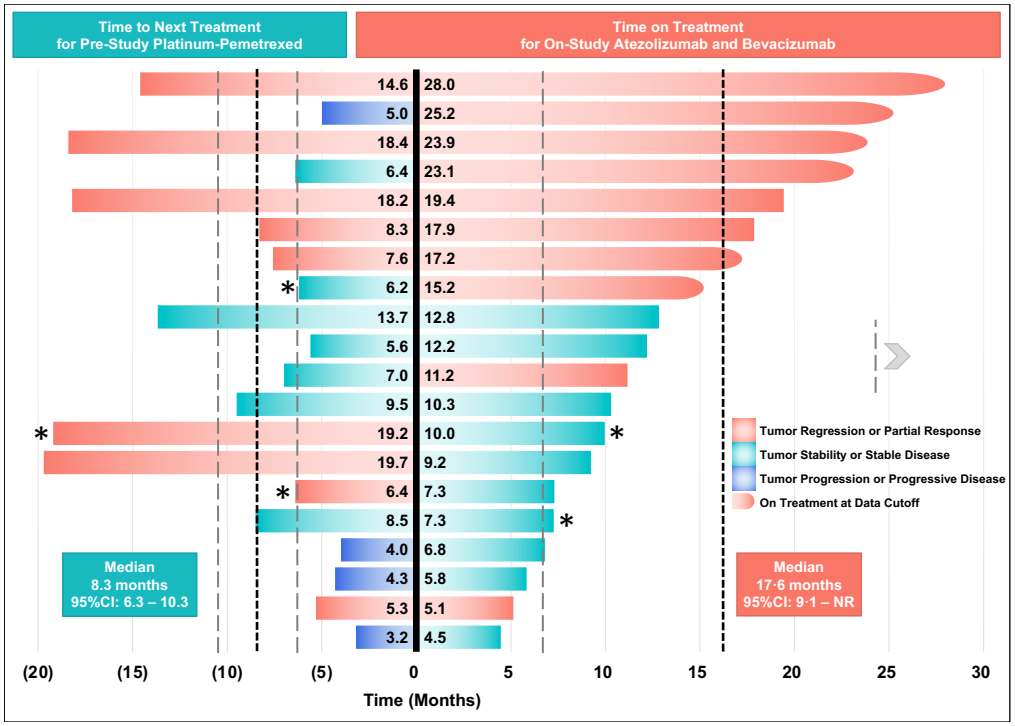
6. **Figure S3. Effect of atezolizumab and bevacizumab (AtezoBev) in patients with malignant peritoneal mesothelioma (MPeM).**

Panel a show a rapid response with decrease in malignant ascites and peritoneal nodule after 3 cycles of AtezoBev. **Panel b** shows a patient with extensive omental carcinomatosis with a long durable response after nearly 2 years of therapy. These cases highlight the prevalence of non-measurable peritoneal disease in MPeM and the robust responses seen with AtezoBev, the extent of which cannot be captured completely with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. **Panel c** illustrates a dramatic metabolic and morphological response seen with AtezoBev in a patient with biphasic mesothelioma (epithelioid and sarcomatoid components). These patients have disease resistant to conventional standard of care cytotoxic chemotherapy (this patient was treated with platinum-pemetrexed chemotherapy prior to study and progressed after 3 cycles at first restaging). **Panel d** shows a young patient with lymph node predominant peritoneal mesothelioma with a significant response on AtezoBev. All these patients had disease that was deemed as refractory to prior platinum-pemetrexed regimen and continue to be on AtezoBev at the time of data cutoff with durable duration of response (range: 12 – 20 months).



7. **Figure S4. Comparison of duration of treatment on atezolizumab and bevacizumab (AtezoBev) on-study with time to next treatment for platinum-pemetrexed based chemotherapy prior to study enrollment.**

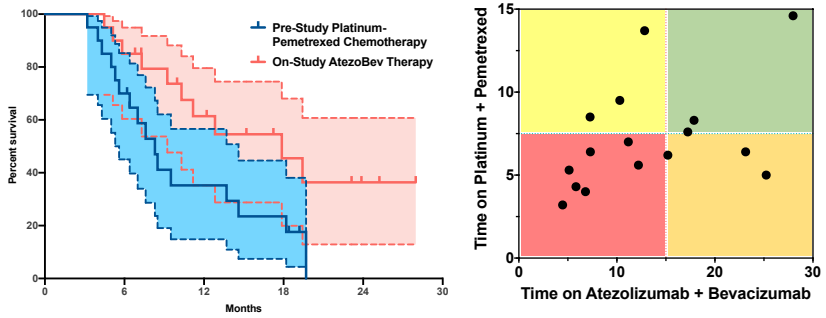
Among 20 patients with malignant peritoneal mesothelioma enrolled on the current study and treated with AtezoBev, time to next treatment (defined as interval from date of initiation of treatment to date of commencement of next line of therapy as per treating physician discretion [obtained from electronic medical records]) on platinum-pemetrexed chemotherapy received as standard of care in comparison to duration of treatment (defined from date of treatment start to discontinuation as per protocol) on AtezoBev. For this real-world evidence, patient-level data was gathered from electronic health records. Vertical dashed lines represent median (black) and 95% confidence intervals (95%CI) (grey) duration. Tumor response (best overall response) on AtezoBev is reported as either partial response, stable disease or progressive disease as per Response Evaluation Criteria in Solid Tumors - version 1.1 by independent radiology review. Tumor response on platinum-pemetrexed chemotherapy prior to study enrollment is reported as either disease regression, stability or progression as per radiology reports and treating physician assessment (obtained from electronic medical records). Asterisk (*) represents patients where treatment was stopped due to toxicity and not due to progressive disease. Patients were censored if treatment was discontinued for any reason other than disease progression.



8. **Figure S5. Comparison of pre-study treatment outcomes (along with historical data) with on-study treatment outcomes for 20 patients with malignant peritoneal mesothelioma.**

For the 20 patients who enrolled on study and treated with atezolizumab and bevacizumab (AtezoBev), the median duration of treatment with AtezoBev (17.6 months; 95%CI: 9.1 – not reached [NR]) was longer than the time to next treatment for these patients on the prior platinum-pemetrexed chemotherapy (8.3 months; 95%CI: 6.3 – 10.3). At end of 1 year, only 30% patients had continued to be on prior chemotherapy compared to 61% of these patients when they were treated with AtezoBev. Furthermore, **prolonged responses occurred on AtezoBev in patient who had both long (green box) and short (orange box) time to next treatment to prior chemotherapy and there was no strong correlation between the two durations** (spearman r = 0.40, P = 0.08). Historical data was taken for chemo-naïve patients on the expanded access program (EAP) for pemetrexed who were treated with platinum-pemetrexed chemotherapy. **The response rate on this historical cohort of EAP population was comparable to our trial patient cohort on similar chemotherapy regimen**.(18)

Comparison of Time to Next Treatment for Pre-Study Platinum-Pemetrexed Chemotherapy with Duration of Treatment On-Study Atezolizumab and Bevacizumab (N = 20)



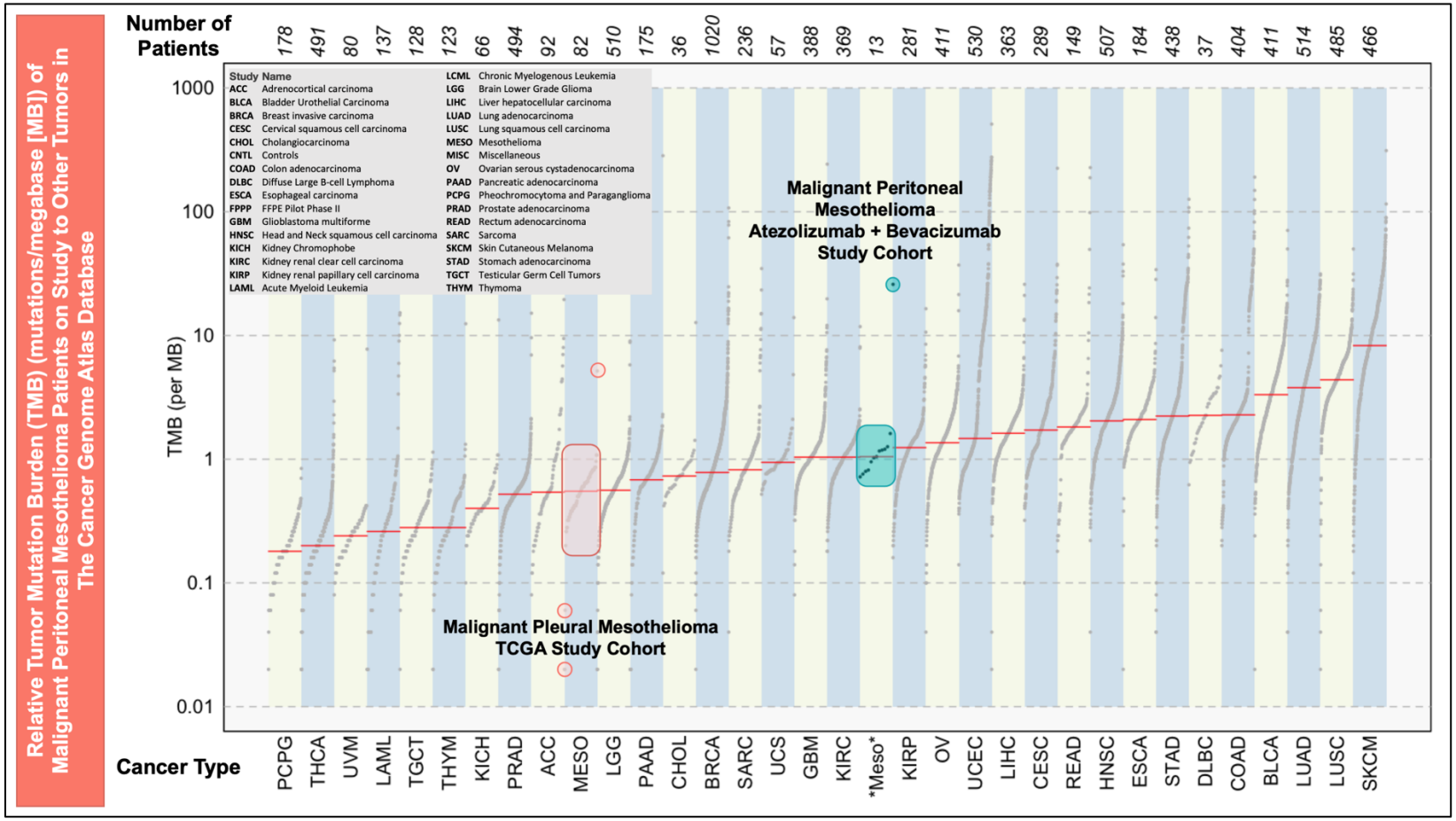
Comparison of Disease Response between Pre-Study Platinum-Pemetrexed Chemotherapy, On-Study Atezolizumab and Bevacizumab and Historical Data on Chemotherapy

Patient Cohorts	For Patients on the Current Study on Atezolizumab and Bevacizumab	For Study Patients on Pre-enrollment Platinum and Pemetrexed Chemotherapy[1]	For Chemo-naïve Patients Reported in the Expanded Access Program on Platinum and Pemetrexed Chemotherapy in MPeM[2]
N	20	20	25
Response[3] % (95%CI)	40% (19.1 – 63.9)	35% (17.9 – 56.8)	28% (12.1 – 49.4)
		P = 0.75	

1. *Tumor response on platinum-pemetrexed chemotherapy prior to study enrollment is reported as either disease regression, stability or progression as per radiology reports and treating physician assessment (obtained from electronic medical records).*
2. *Response data was reported for the subset of patients with malignant peritoneal mesothelioma (25 of 98) who were chemo naïve.*

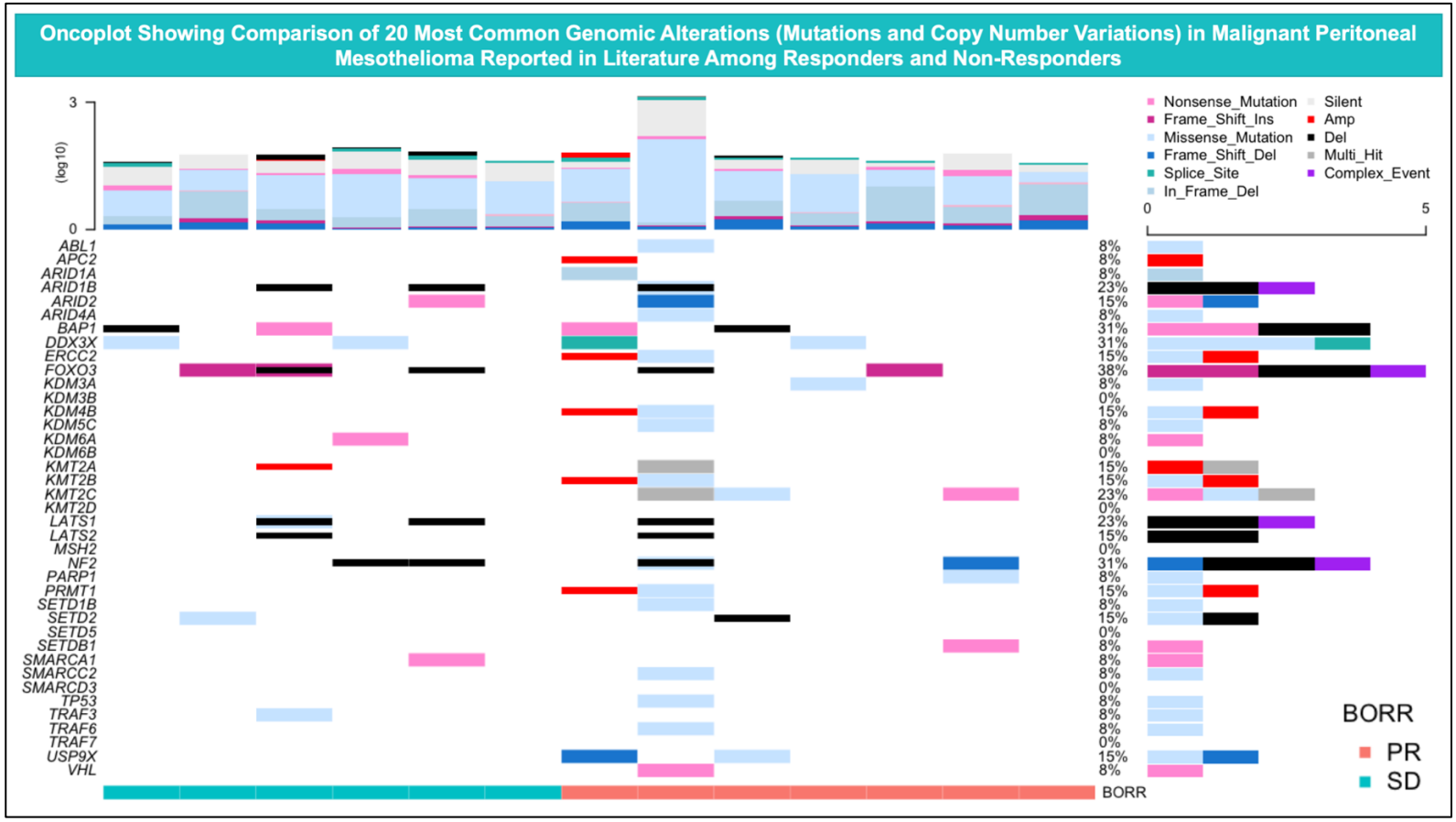
9. Figure S6. Tumor mutation burden (TMB) of patients with malignant peritoneal mesothelioma on current study relative to other tumors as derived from The Cancer Genome Atlas Database (TCGA).

TMB was calculated as mutations per megabase (MB) for our cohort as per supplementary methods 1 and obtained from TCGA for other tumor types. **TMB for our study cohort of malignant peritoneal mesothelioma was low with a median TMB of 0.8 mutations/megabase**. Compared to patients with malignant pleural mesothelioma, TMB appears to be slightly higher.



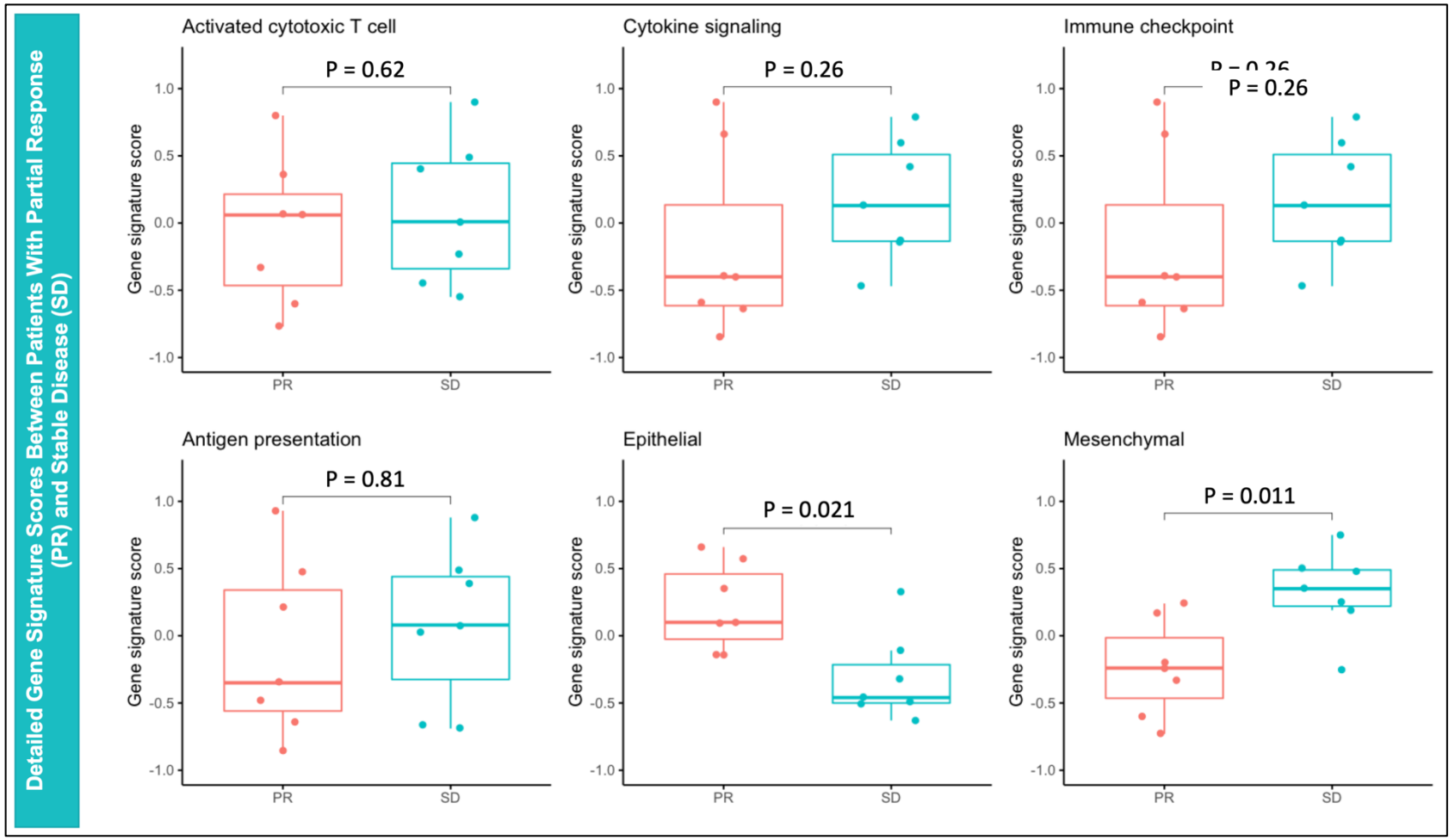
10. Figure S7. Comparison of 20 Most Common Genomic Alterations in Malignant Peritoneal Mesothelioma (MPeM) Reported in Literature Among Responders and Non-Responders on Trial

Oncoplot shows 20 most common genes altered (mutations and copy number variations) in patients with MPeM reported in literature. Each column represents a patient. Patients are arranged in order of best percentage change (response) in tumor measurements from baseline (from left to right: increase to decrease) as per RECISTv1.1 (Response Evaluation Criteria in Solid Tumors - version 1.1). The color bar at bottom shows response for each patient (PR [responder] and SD [non-responder with stable disease]). Each row represents a gene. The barplot on top shows the number of mutations (log) for each patient and the barplot on right has the frequency of mutations in all patients in each gene. Colors in the heatmap indicates distinct types of alterations as per key. **No specific genomic alterations appeared to be associated with response.**



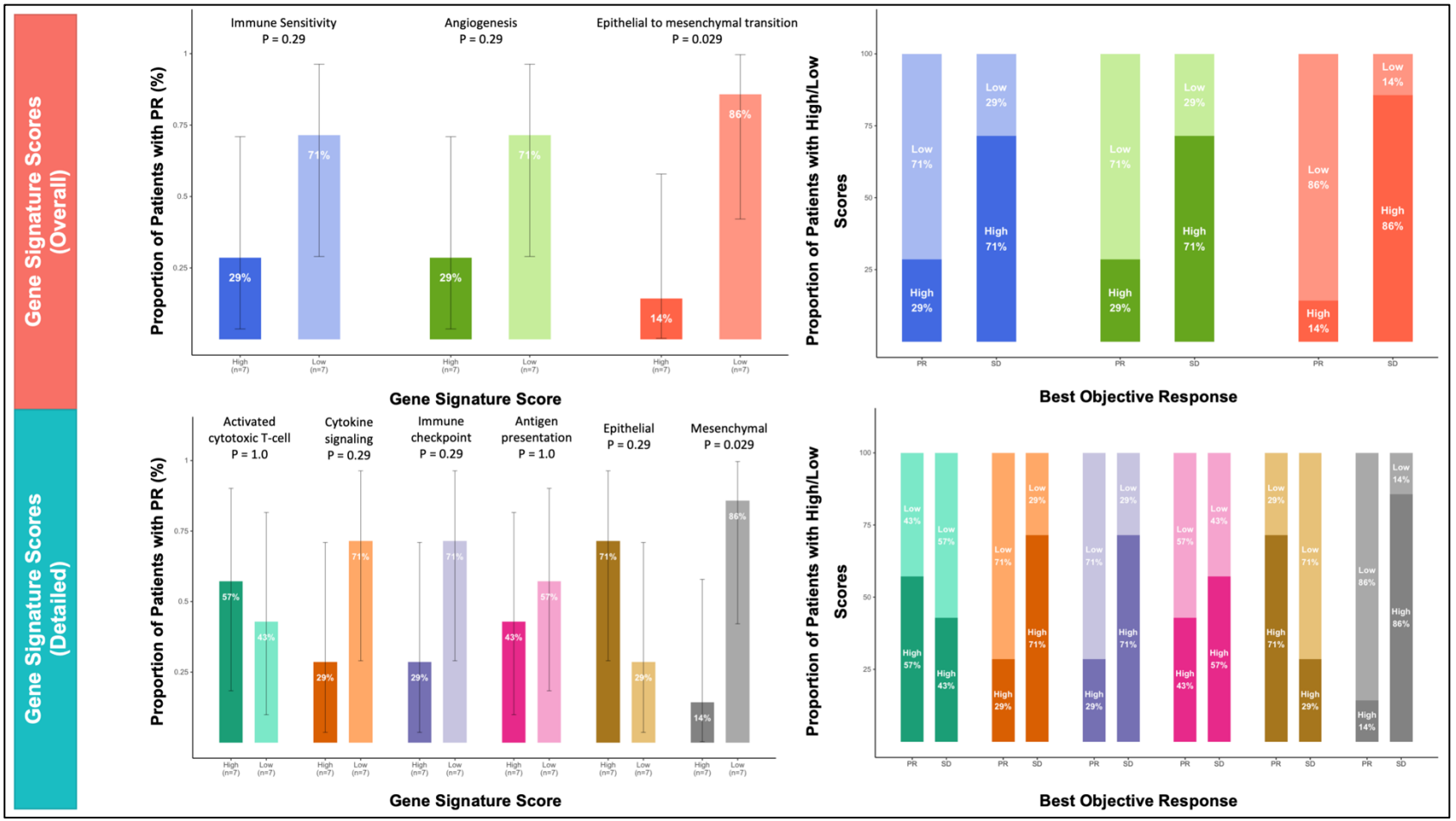
11. Figure S8. Detailed Gene Signature Scores in Pre-treatment Tumor Tissue Between Responders (Patients with Partial Response [PR]) and Non-responders (Patients with Stable Disease [SD]).

Gene signatures described in supplemental methods 1 were based on previously published associations with immune-sensitivity, angiogenesis and epithelial-mesenchymal transition (EMT) and have been shown to predict responsiveness to immune checkpoint inhibition and VEGF blockade.(12-14) Scores for each patient-sample were calculated using normalized counts. **Median epithelial and mesenchymal gene scores were different between responders and non-responders, but no apparent difference was seen in immune or angiogenic scores.**



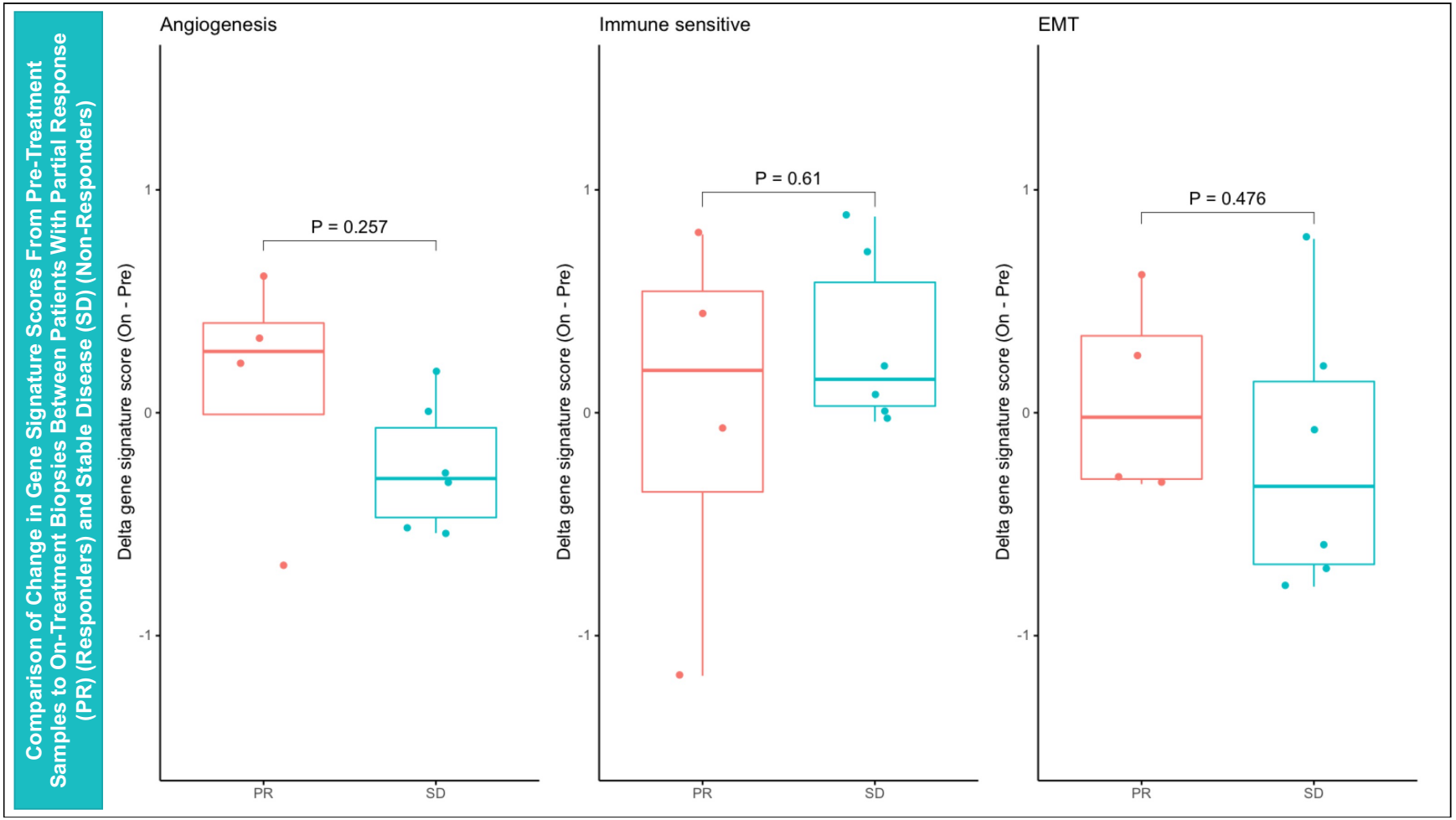
12. Figure S9. Association between Gene Signature Scores in Pre-treatment Tumor Tissue and Response Status (Responder (Patients with Partial Response [PR]) vs. Non-responders (Patients with Stable Disease [SD]).

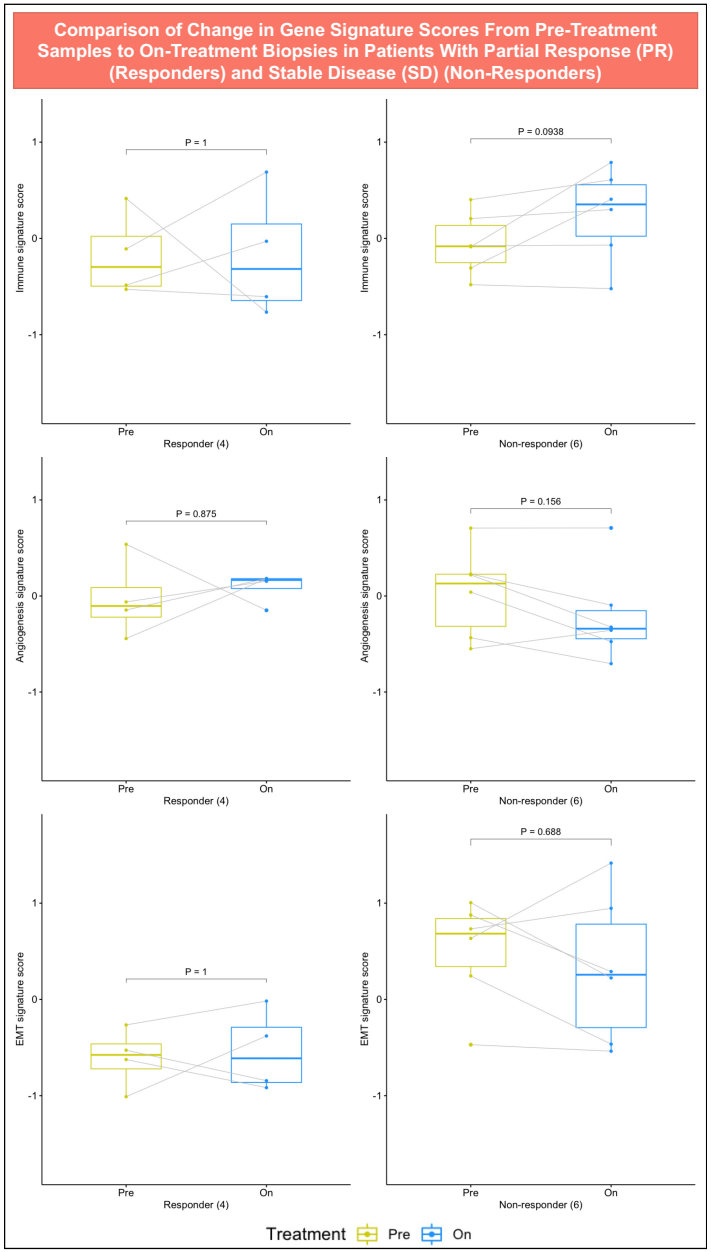
Gene signatures were calculated as previously described. Patients were divided into two groups using median gene signature score of all samples as cutoff. High expression was defined as expression at or above median levels and low expression was defined as expression below the median. Response status was determined as per Response Evaluation Criteria in Solid Tumors - version 1.1. Differences between groups was assessed using Fisher's exact test.



13. Figure S10. Association between change in gene signature scores between baseline and on-treatment samples and response to therapy with atezolizumab and bevacizumab.

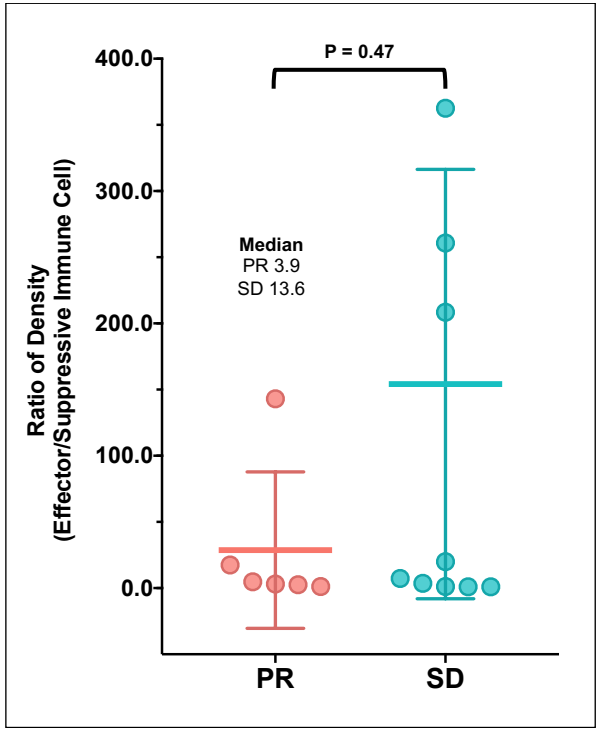
Gene signatures based on previously published associations with immune-sensitivity, angiogenesis and epithelial-mesenchymal transition (EMT) were calculated for 2 samples (pre-treatment [Pre] and on-treatment [On]) per patient as described in supplemental methods 1.(12-14) Change in gene signature scores was calculated as difference between on-treatment and pre-treatment score. **No significant change in gene signature scores was found between responders (PR) and non-responders (SD).**




Comparison of Change in Gene Signature Scores From Pre-Treatment Samples to On-Treatment Biopsies in Patients With Partial Response (PR) (Responders) and Stable Disease (SD) (Non-Responders)
Immune signature score
P = 1
Pre
On
Responder (4)
P = 0.0938
Non-responder (6)
Angiogenesis signature score
P = 0.875
P = 0.156
EMT signature score
P = 1
P = 0.688
1
0
-1
Treatment
Pre
On

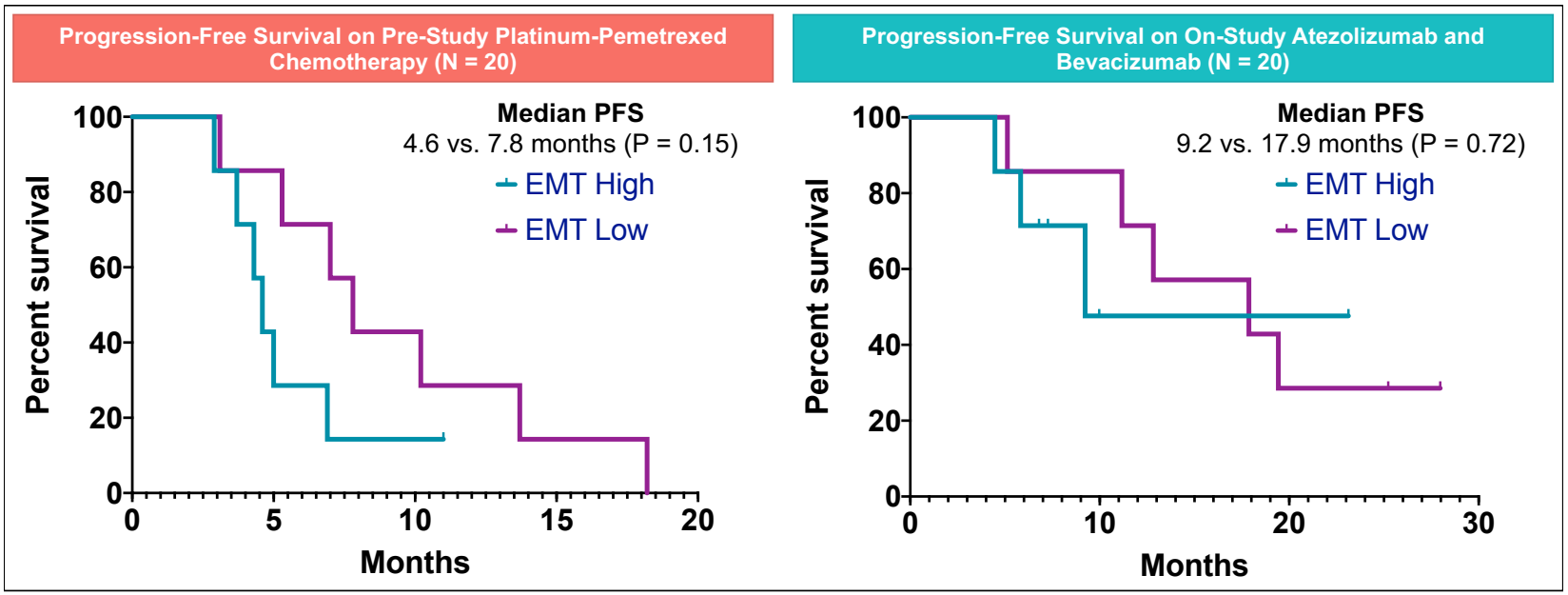
14. **Figure S11. Ratio of density of immune-effector cells and immune-supressor cells its association with response on atezolizumab and bevacizumab on study.**

Immune-effector cells were defined as cytotoxic T-cells (CD3+CD8+) and immune-suppressor cells were defined as regulatory T-cells (CD3+FOXP3+) identified by using multiplex immunofluorescence as described in supplementary methods previously. **No significant difference was seen between responders (PR) and non-responders (SD)**.



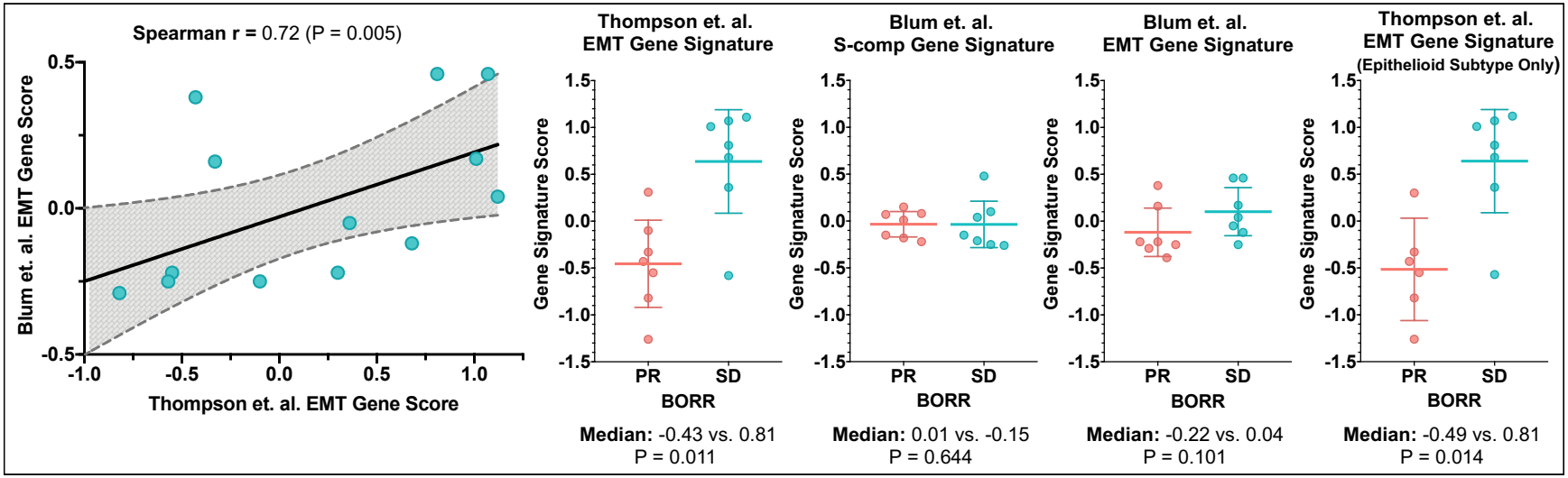
15. Figure S12. Association between epithelial-mesenchymal transition (EMT) gene score and progression-free survival (PFS) in study cohort.

Baseline EMT gene signature score was calculated using pre-treatment tissue (prior to treatment with AtezoBev on study) as previously described. Patients were classified as having EMT High (more mesenchymal) and EMT Low (more epithelial) phenotypes. PFS was evaluated for both pre-study platinum-pemetrexed chemotherapy and for on-study atezolizumab and bevacizumab therapy. **EMT high patients appeared to have poorer PFS with both treatments**, although this difference was not statistically significant. These patients possibly represent an aggressive tumor biology.



16. Figure S13. Association between epithelial-mesenchymal transition (EMT) gene signature score used in our study and EMT signature derived from published studies in malignant pleural mesothelioma (MPM) and response. (14,19)

Using meta-analysis of transcriptomic profiles from published classifications in MPM, Blum et. al. highlighted two main groups of highly correlated clusters within all datasets which corresponded to most extreme epithelioid (E-comp) and sarcomatoid (S-comp) phenotypes. Gene signature score corresponding to genes that correlated with S-comp phenotype and EMT gene signature score using EMT genes in S-comp molecular component was calculated using pre-treatment tissue and correlated with EMT gene signature score calculated using gene set as previously described and with best objective response rate (BORR) classified as responder (partial response, PR) and non-responder (stable disease, SD) as per RECISTv1.1. **EMT gene scores showed strong correlation and although not statistically significant, similar trend (responders had lower EMT gene signature scores indicating a more epithelial phenotype and non-responders had higher EMT gene signature scores indicating a more mesenchymal phenotype) with regards to response.**

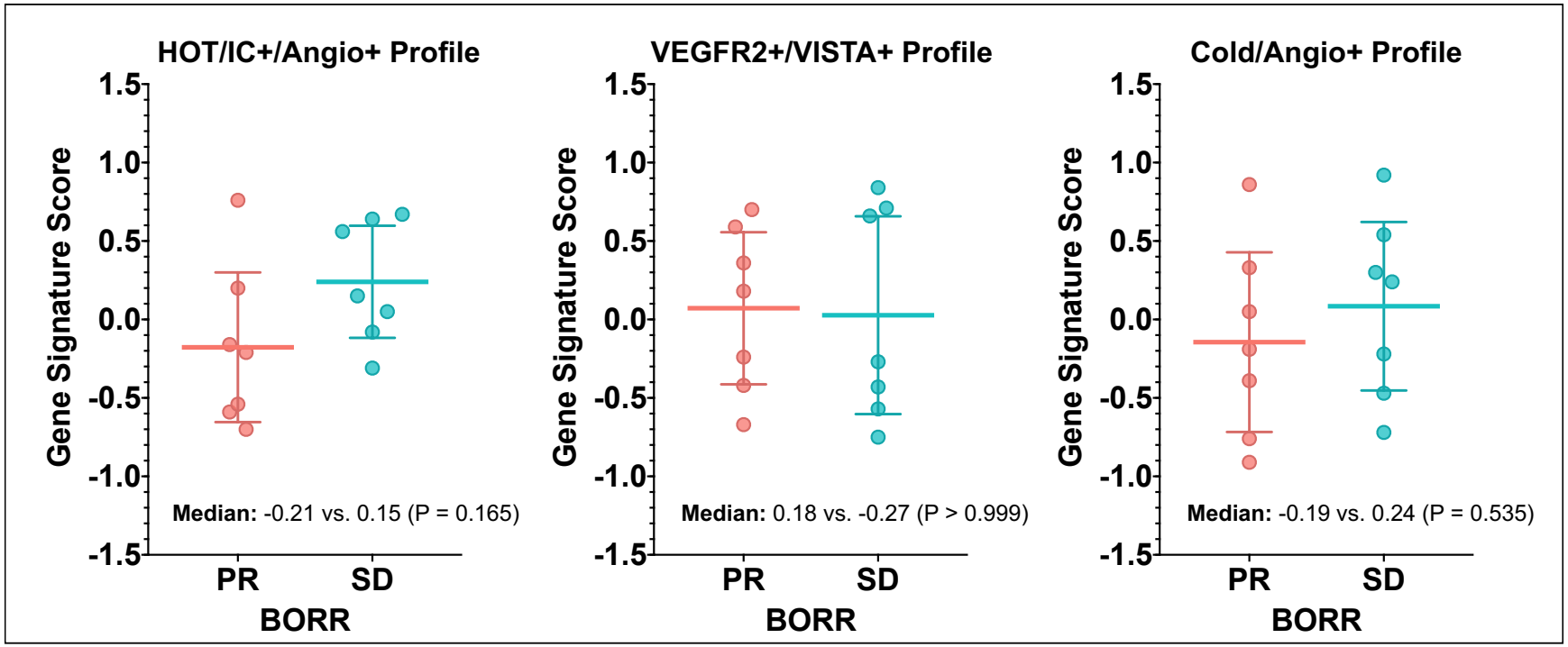


1. *Thompson et. al. Gene Set (Lung Cancer, 2020): EMT score = $Score_{Mesenchymal}$ - $Score_{Epithelial}$ (Mesenchymal genes: AGER, FN1, MMP2, SNAI2, VIM and ZEB2; Epithelial genes: CDH1, CDH3, CLDN4, EPCAM, MAL2 and ST14)*

2. *Blum et. al. EMT Gene Set (Nature communications, 2019): EMT score = Score of genes (EMT genes: ACVRL1, CCND1, COL1A1, CTNNB1, EZH2, GDNF, GLIPR2, HEY1, HEYL, HIF1A, NOG, NOTCH1, NRP1, RBPJ, SNAI2, SOX9, TGFB1, TGFB1I1, TWIST1 and WNT5A)*

17. **Figure S14. Association between response and prognostic transcriptomic profiles published for malignant pleural mesothelioma (MPM).(20)**

Alcala and colleagues reported three distinct transcriptomic profiles with prognostic and therapeutic implications: 1) Hot/IC+/Angio+ profile that is characterized by high expression of pro-angiogenic genes (*VEGFR1*, *VEGFR3*, and *PDGFRB*) and immune-checkpoints (ICs) (*PD(L)1*, *CTLA4*, *TIM3*, and *LAG3*) and short survival; 2) VEGFR2+/VISTA+ profile that has high expression levels of *VEGFR2* and *VISTA* and shows best median survival; and 3) Cold/Angio+ profile with high expression of pro-angiogenic genes (*VEGFR1*, *VEGFR3*, and *PDGFRB*) and show poor survival. We calculated a gene signature score corresponding to each of these profiles and compared these between responders (partial response, PR) and non-responders (stable disease, SD) based on best objective response rate (BORR) per RECISTv1.1. **No clear predictive impact was seen with any of these profiles using this prognostic signature.**



18. Table S1. Key trials showcasing activity of immune checkpoint and VEGF inhibition in malignant mesothelioma.

Trials include those that enrolled patients with either malignant pleural (MPM) or peritoneal mesothelioma (MPeM).

Study	Immune Checkpoint Inhibitor	Clinical Trials Identifier	Year	PMID	Total Evaluable (N)	Was MPeM Patients Eligible / Enrolled	MPeM (N)	RR (%)	RR in MPeM (%)	PFS (m)
University of Chicago (21)	Pembrolizumab	NCT02399371	2018	OA08.03 (JTO)	65	Yes / Yes	8	19.0%	12.5%	4.5
Keynote 028 (22)	Pembrolizumab	NCT02054806	2017	28291584	25	No / No	-	20.0%	-	5.4
JAVELIN (23)	Avelumab	NCT01772004	2019	30605211	53	Yes / No	-	9.0%	-	4.1
INITIATE (24)	Nivolumab + Ipilimumab	NCT03048474	2019	30660511	34	No / No	-	29.0%	-	6.2
IFCT1501MAPS2 (25)	Nivolumab	NCT02716272	2019	30660609	62	No / No	-	17.5%	-	4.0
IFCT1501MAPS2 (25)	Nivolumab + Ipilimumab	NCT02716272	2019	30660609	63	No / No	-	25.8%	-	5.6
University Hospital Siena (26)	Tremelimumab	NCT01649024	2013	24035405	29	Yes / Yes	1	7.0%	NR	6.2
PROMISE-meso (27)	Pembrolizumab	NCT02991482	2020	32976938	73	No / No	-	22.0%	-	2.5
Study	**VEGF Inhibitor**	**Clinical Trials Identifier**	**Year**	**PMID**	**Total Evaluable (N)**	**Was MPeM Patients Eligible / Enrolled**	**MPeM (N)**	**RR (%)**	**RR in MPeM (%)**	**PFS (m)**
Jackman et al (28)	Bevacizumab	-	2008	18543326	24	No / No	-	0.0%	-	2.2
CALGB30307 (29)	Sorafenib	NCT00651456	2010	20736856	30	Yes / Yes	3	3.3%	-	3.7
CALGB30107 (30)	Vatalanib	NCT00053885	2012	22197613	46	Yes / Yes	3	6.4%	-	4.1

Abbreviations: *m, months; N, number of patients; NR, not reported; PFS, median progression-free survival; RR, response rate*

19. Table S2. Secondary endpoints per immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST) by independent review.(31)

Endpoint	Patients (N) (%)
Confirmed objective response rate (ORR) – patients with confirmed complete or partial response (N = 20)	9 of 20 (45%) (95%CI: 23.1 – 68.5)
Disease Control Rate (DCR) – patients with confirmed response or stable disease (N = 20)	18 of 20 (90%) (95%CI: 68.3 – 98.8)
Duration of response (DoR) (median) – for all responders (N = 9)	12.0 months (range: 2.3 – 20.6)
Progression-free survival (PFS) (median) – for all patients (N = 20)	17·6 months (95%CI: 9·1 – not reached [NR])

Abbreviations: *95%CI, 95% confidence interval*

20. Table S3. Treatment-related adverse events (TRAEs)

Listed TRAEs are those of any grade that occurred on study in ≥ 10% patients and all grade ≥ 3 events. All TRAEs are coded and graded as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Adverse Event	All Grades	%	Grade 1	%	Grade 2	%	Grade ≥ 3	%
Hypertension	12	60			6	30	8	40
Fatigue	8	40	4	20	2	10	1	5
Anorexia	6	30	6	30				
Proteinuria	6	30	5	25	6	30		
Constipation	5	25	4	20	1	5		
Lymphocyte count decreased	5	25	3	15	3	15		
Nausea	5	25	4	20	2	10		
Pruritus	5	25	4	20	1	5		
Arthralgia	4	20	4	20				
Diarrhea	4	20	4	20				
Epistaxis	4	20	4	20				
Vomiting	4	20	4	20	1	5		
Weight loss	4	20	3	15	1	5		
Abdominal Pain	3	15	1	5	1	5	1	5
Creatinine increased	3	15	3	15				
Dry mouth	3	15	3	15				
Dry skin	3	15	3	15				
Headache	3	15	3	15				
Mucositis	3	15	2	10	1	5		
Myalgia	3	15	3	15				
Peripheral sensory neuropathy	3	15	3	15				

Rash - maculopapular	3	15	3	15				
Anemia	2	10	1	5			2	10
Platelet count decreased	2	10	1	5			1	5
Aspartate aminotransferase increased	2	10	1	5	1	5		
Bruising	2	10	2	10				
Dehydration	2	10			2	10		
Dysgeusia	2	10	2	10				
Dyspnea	2	10	2	10	1	5		
Eye disorders - Other, specify	2	10	2	10				
Hoarseness	2	10	2	10				
Hypomagnesemia	2	10	2	10				
Hypothyroidism	2	10			2	10		
Alanine aminotransferase increased	1	5					1	5
Ileus	1	5					1	5
Pancreatitis	1	5					1	5
Thromboembolic event	1	5					1	5

21. Table S4. Key trials comparing activity of atezolizumab and bevacizumab (AtezoBev) in current trial to that of available treatment options for patients with malignant (peritoneal) mesothelioma.

Trial	Current Study	Involving Immune Checkpoint Inhibitors					Involving Bevacizumab			Involving Chemotherapy
Therapy	**AtezoBev**	**Avelumab**	**Pembrolizumab**	**Nivolumab**	**Nivolumab + Ipilimumab**	**Tremelimumab**	**Bevacizumab with Gemcitabine + Cisplatin**	**Bevacizumab with Cisplatin + Pemetrexed**	**Bevacizumab with Erlotinib**	**Gemcitabine + Vinorelbine**
Arm(s)	Single	Single	Single	Two	Two	vs. Placebo	vs. Placebo	vs. Placebo	Single	Single
Disease	MPeM	Both	MPM	MPM	MPM	Both	Both	MPM	MPM	MPM
Line of Therapy	>1st	>1st	>1st	>1st	2/3rd	2/3rd	>1st	>1st	>1st	2nd
Level of Evidence	Phase 2	Phase 1b	Phase 1b	Phase 2	Phase 2	Phase 3	Phase 2R	Phase 3	Phase 2	Phase 2
Total N	20	53	25	62	63	571	108	448	24	30
Treated MPeM (N)	20	NRp	0	0	0	18	9	0	0	0
RR (%)	40	9	20	18.5	25.9	4.5 (1.1)	24.5 (22)	NRp	0	10
95%CI	19-64	3-20	7-41	8-28	14-38	3-7	NRp	NRp	0-16	2-26

mPFS (months)	17.6	4.1	5.4	4	5.7	2.8 (2.7)	6.9 (6)	9.2 (7)	2.2	2.8
95%CI	9.1-NR	1-6	3-7	3-6	3-10	2-3	5-7	9-11	1-6	0.6-12.1
mOS (months)	NR	10.7	18	11.9	15.9	7.7 (7.3)	15.6 (15)	18.8 (16)	5.8	10.9
95%CI	18-NR	7-20	9-NR	7-17	11-22	7-9	10-19	16-23	3-10	0.8-25.3
1-yr OS (%)	85	44	63	49	58	NS	58 (57)	NRp	NRp	44
DCR (%)	93	58	90	40	52	28 (22)	51 (60)	NRp	50	82
References	**2016-0861**	**JAVELIN(23)**	**KEYNOTE-028(22)**	**MAPS-2 Trial (25)**	**MAPS-2 Trial(25)**	**DETERMINE(32)**	**Kindler JCO 2012(33)**	**MAPS Trial(34)**	**Jackman Cancer 2008(28)**	**Zucali Cancer 2008(35)**

Abbreviations: *95%CI, 95% confidence interval; DCR, disease control rate; MPeM, malignant peritoneal mesothelioma; MPM, malignant pleural mesothelioma; N, number of patients; NR, not reached; NRp, not reported; mOS, median overall survival; mPFS, median progression-free survival; RR, response rate*

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