UNICANCER/IFCT

PROTOCOL SAFIR 02 Lung
Sponsor N° : UC 0105-1305 / IFCT 1301
EudraCT N° : 2013-001653-27

Evaluation of the efficacy of high throughput genome analysis as a therapeutic decision tool for patients with metastatic non-small cell lung cancer

Version n°6 30th Octobre 2017

SUBSTANTIAL AMENDMENT	CPP Approval	ANSM Approval	VERSION
INITIAL PROTOCOL	09/11/2013	10/17/2013	Version 1.0 – July 2013
AMENDMENT 2	03/20/2014	03/25/2014	Version 2.0 – January 17th 2014
AMENDMENT 4	01/09/2015	01/07/2015	Version 3.0 – September 1st 2014
AMENDMENT 6	09/24/2015	09/09/2015	Version 4.0 – May 20th 2015
AMENDMENT 7 (URGENT SAFETY MEASURE)	12/08/2015	11/16/2015	Version 4.1 – October 7th 2015
AMENDMENT 11	09/06/2016	09/09/2016	Version 5.0 – June 17th 2016
AMENDMENT 15	09/19/2018	03/12/2018	Version 6.0 –October 30th 2017

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APPROVAL AND CONTACT DETAILS
PROTOCOL SAFIR02 Lung

Evaluation of the efficacy of high throughput genome analysis as a therapeutic decision tool for patients with metastatic non-small cell lung cancer

COMPETENT AUTHORITY	**Agence nationale de sécurité du médicament et des produits de santé (ANSM)**	**Date of authorization : 10/17/2013**
		Ref. ANSM : 130975A-12
FRENCH ETHIC COMMITTEE	**Name of the Committee for the Protection of Persons (CPP): CPP IDF2,** **Hôpital Necker** **Porte N2 1er étage** **149, rue de Sèvres** **75749 Paris Cedex 15**	**Date of approval : 09/11/2013**
		Ref. CPP : 2013-08-04

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SYNOPSIS – PROTOCOL SAFIR02 Lung

A) CLINICAL TRIAL IDENTIFICATION

SPONSOR - PROTOCOL CODE NUMBER : UC-IFCT-0105/1305

EUDRACT N° : 2013-001653-27
VERSION & DATE : Version n°6.0-October 30th 2017

TRIAL TITLE: Evaluation of the efficacy of high throughput genome analysis as a therapeutic decision tool for patients with metastatic non-small cell lung cancer.

ABBREVIATED TITLE : SAFIR 02 Lung

PRINCIPAL INVESTIGATOR : PR FABRICE BARLESI
Gustave Roussy

PLANNED NUMBER OF INVESTIGATIONNAL SITES : 37	**NUMBER OF PATIENTS :** **1350 FOR THE SCREENING PHASE** **230 FOR THE RANDOMIZED TARGETED SUBSTUDY (SUBSTUDY 1)** **180 FOR THE RANDOMIZED IMMUNE SUBSTUDY (SUBSTUDY 2)**

B) SPONSOR IDENTIFICATION

NAME OF THE INSTITUTION : UNICANCER

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C) TRIAL GENERAL INFORMATION

MEDICAL CONDITION:
Patients with metastatic non-small cell lung cancer (NSCLC) in 1st line chemotherapy

METHODOLOGY:
This is an open-label multicentric randomized phase II trial, using high throughput genome analysis as a therapeutic decision tool, aimed at comparing a targeted treatment administered according to the identified molecular anomalies of the tumor with a standard maintenance as per guidelines (targeted substudy 1) as well as immunotherapy versus maintenance therapy in patients without actionable genomic alterations or non eligible to substudy 1. (immune substudy 2)

PRIMARY OBJECTIVE :
To evaluate whether treatment with targeted agents guided by high throughput molecular analysis (CGH array, next generation sequencing) improves progression-free survival as compared to standard maintenance therapy in patients with metastatic NSCLC.

C) TRIAL GENERAL INFORMATION (…)

SECONDARY OBJECTIVES :

- To compare progression-free survival in patients treated with anti-PDL1 antibody (durvalumab) with those treated with maintenance therapy, in patients without actionable genomic alteration in the immune substudy 2 (primary objective of the substudy 2).
- To compare overall survival in each substudy.
- To compare overall response rates and changes in tumor size in each substudy.
- To evaluate safety, in each substudy
- To explore the efficacy (response rate, change in tumor size, progression-free survival, overall survival) and safety of each individual targeted agent in substudy 1.
- To perform a prospective pooled analysis of SAFIR02 Lung and SAFIR02 Breast studies
- To correlate molecular characteristics in patients with the efficacy endpoints (response rate, progression-free and overall survival) in each substudy.

ADDITIONAL RESEARCH OBJECTIVES /COMPANION STUDIES :

1/ Circulating tumor DNA analysis to investigate: a/ correlation of ctDNA profiles with those obtained with NGS in the tumor sample; b/ identification of molecular alterations linked to resistance to targeted therapies.

2/ Validation of the functional protein activation and exploration of the sequence of events in the signalling pathways, using FISH and CISH, IHC staining, kinome arrays and RPPA analysis.

3/ Investigation of molecular changes that underlie disease progression and the formation of metastases a/ using whole exome sequencing program on normal cells, primary and metastatic tumor material; b/ comparing the variation on molecular profiles from different metastatic sites

4/ Construction of a virtual cell to develop the optimal algorithm able to identify the driver alterations and then to deliver the optimal choice of therapy.

SCREENING PHASE

INCLUSION CRITERIA:

1. Patients with histologically proven NSCLC
2. Metastatic relapse or stage IV at diagnosis, or stage IIIb not amenable to surgery or radiotherapy
3. No EGFR-activating mutation or ALK translocation for non-squamous NSCLC patients below 15 pack-year. For non squamous NSCLC patients above 15 pack-year and patients with squamous NSCLC, EGFR and ALK status are not mandatory at the time of inclusion but will need to be confirmed before randomization
4. Patients with primary tumor or metastases that can be biopsied, excluding bone metastases. In the case a fresh biopsy collection is not achievable, patients able to provide a FFPE biopsy sample or FFPE cytoblock will be considered as well. Circulating tumor (ct) ADN, ideally collected before chemotherapy initiation, will be a tertiary option in the following situation : existing tissue (fresh or FFPE) is not eligible for the study (i.e. <30% tumor cells, or insufficient size) AND patients can not undergo a new biopsy (e.g. inaccessible location, or bone disease as the sole site, or patient real safety concerns)
5. Age > 18 years
6. WHO Performance Status 0/1
7. Chemo-naïve patients for their NSCLC management eligible to a first line platinum-based chemotherapy or currently receiving a first line platinum-based chemotherapy with a maximum of 2 cycles at the time of biopsy
8. No tumor progression observed with the current line of treatment
9. Presence of a measurable target lesion or evaluable disease according to RECIST criteria v1.1
10. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses
11. Patient with social insurance coverage.

EXCLUSION CRITERIA:

1. Spinal cord compression and/or symptomatic or progressive brain metastases (unless asymptomatic or treated and stable without steroids during the last 30 days)
2. Patients with all target lesions in a previously irradiated region, except if clear progression has been observed prior to study in at least one of them
3. Patients who already had a genomic profile (both CGH and NGS analysis) in which no SAFIR02 targetable alterations have been identified
4. Inability to swallow
5. Major problem with intestinal absorption
6. Any of the following cardiac criteria:
   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG
   - Any factors increasing the risk of QTc prolongation or arrhythmic events such as heart failure, hypokalaemia, potential for torsades de pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years old or any concomitant medication known to prolong the QT interval
   - Experience of any of the following procedures or conditions in the preceding 12 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, past or current uncontrolled angina pectoris (Canadian Cardiovascular Society grade II-IV despite medical therapy), congestive heart failure NYHA Grade ≥2, torsades de pointes, current uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy), cardiomyopathy
7. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which requires steroid treatment or any evidence of clinically interstitial lung disease
8. Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin
9. Evidence of severe or uncontrolled systemic disease (active bleeding diatheses, or active Hepatitis B, C and HIV or any other serious active infection)
10. Previous history of myelodysplastic syndrome or acute myeloid leukaemia
11. Medical diagnosis of acne rosacea, severe psoriasis and severe atopic eczema
12. Prior exposure to anthracyclines or mitoxantrone with cumulative exposure in excess of 360 mg/m² for doxorubicin, 720 mg/m² for epirubicin, or 72 mg/m² for mitoxantrone (e.g for any other type of cancer occurred more than 5 years ago)
13. History of retinal degenerative disease, eye injury or corneal surgery in the previous 3 months, past history of central serous retinopathy or retinal vein occlusion, intraocular pressure >21 mmHg, or uncontrolled glaucoma
14. Women who are pregnant
15. History of heamorrhagic or thrombotic stroke, TIA or other CNS bleeds
16. Renal disease including glomerulonephritis, nephritic syndrome, Fanconi syndrome, renal tubular acidosis
17. Patients using drugs that are known potent inhibitors or potent inducers or substrates of cytochrome P450 are not eligible if those treatments cannot be substituted during the randomized phase of the study
18. Any condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol including recent history (past 12 months) of drug abuse or alcohol abuse
19. Individuals deprived of liberty or placed under the authority of a tutor

RANDOMIZED PHASE

SUBSTUDY 1: TARGETED THERAPIES VERSUS MAINTENANCE THERAPY

INCLUSION CRITERIA

1. Patients who received 4 cycles of an induction platinum-based chemotherapy and who are presenting a stable or a responding disease at the time of randomization
2. Patients who still meet the screening phase inclusion and exclusion criteria
3. EGFR and ALK status should be confirmed negative for all patients at this point
4. Patients whose tumor sample is presenting at least one genomic alteration from the list of predefined targetable genomic alterations and for whom the Molecular tumor board has provided a personalized guidance
5. Age > 25 years for patients planned to receive **AZD4547**
6. Patients will have had at least a 28-day washout period from the platinum-based regimen prior to randomization and should have recover (grade ≤1) from all residual toxicities, excluding alopecia
7. Potentially reproductive patients must agree to use an effective contraceptive method (acceptable methods of contraception are described in section 9.1.1 and 10.1.1 of the protocol) while on treatment, beginning 2 weeks before the first dose of investigational product and for at least 4 months after the last dose of study drug. Male patients should refrain from fathering a child or donating sperm during the study and for at least 4 months following the last dose of study treatment
8. Women of childbearing potential must have a negative serum pregnancy test done within 14 days and/or urine pregnancy test 72 hours prior to the administration of the study drug
9. Women who are breastfeeding should discontinue nursing prior to the first dose of study drug and until 3 months after the last dose
10. Provision of signed and dated, written informed consent prior to randomization and to any study specific procedures, sampling and analysis.
11. For patients supposed to be treated by savolitinib, adequate liver function defined as:

    -Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) with TBL≤ 1x ULN

    -OR TBL >ULN-≤1.5x ULN with ALT and AST ≤ 1x ULN

EXCLUSION CRITERIA

1. No “targetable” genomic alteration identified during the screening phase (either due to the lack of alteration or due to ineligible samples for genomic analysis) or unfavorable decision from the Molecular tumor board to drive the patient to the randomization
2. Life expectancy < 3 months
3. Disease progression occurring at any time during chemotherapy and before randomization or toxicity that led to the discontinuation of the platinum-based chemotherapy before 4 full cycles have been delivered
4. Major surgery within 30 days (excluding placement of vascular access) or minor surgery within 14 days prior to randomisation
5. Less than 28 days from radiotherapy (wide field of radiation), less than 2 weeks from palliative radiation (limited fields). Fields should not have involved all target lesions
6. Patients previously treated for their metastatic disease with a targeted agent, the same or in the same class as the agent to be given to the patient in substudy 1
7. Participation to another clinical study with an investigational product (IP) during the last 30 days
8. History of hypersensitivity to active or inactive excipients of one of the study drugs
9. Toxicities of grade ≥2 from any previous anti-cancer therapy, with the exception of alopecia
10. Altered haematopoietic or organ function, as indicated by the following criteria:
    - Polynuclear neutrophils < 1.5 x 10^9/L
    - Platelets < 100 x 10^9/L
    - Haemoglobin < 90 g/L (or Haemoglobin < 100 g/L and no blood transfusion within 28 days for

olaparib)
- ALAT/ASAT > 2.5x ULN in the absence of or > 5x ULN in the presence of liver metastases
- bilirubin > 1.5xULN
- creatinine clearance ≤50 mL/min (measured or calculated by Cockroft and Gault formula)
- Proteinuria > 3+ on dipstick analysis or > 3.5g/24 hours or a urine protein/creatinine ratio > 3.5 (only for patients dried to receive AZD5363)
- Sodium, magnesium, calcium and phosphate > ULN and < LLN
- Potassium < LLN or > ULN (or Potassium < 4 mmol/L or > ULN for vandetanib)

11. Any of the following additional cardiac criteria:
    - Mean resting corrected QT interval (QTc)>480msec (or QTcF >450 msec) obtained from 3 consecutive ECGs
    - LVEF <55% (MUGA scan or Echocardiogram)
12. Altered ophthalmic conditions confirmed by an ophthalmology specialist for patients likely to be treated with :
    - AZD4547 : current evidence or previous history of retinal pigmented epithelium detachment (RPED), previous laser treatment or intra-ocular injection for treatment of macular degeneration, current evidence or previous history of dry or wet age-related macular degeneration, current evidence or previous history of retinal vein occlusion (RVO), current evidence or previous history of retinal degenerative diseases (eg, hereditary), current evidence or previous history of any other clinically relevant chorioretinal defect
    - Selumetinib : intraoccular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure), current or past history of retinal pigment epithelial detachment or central serous retinopathy or retinal vein occlusion
13. Clinically significant abnormalities of glucose metabolism, for patients supposed to be treated by vistusertib or AZD5363, as defined by any of the following:
    - For vistusertib :
    - Diagnosis of diabetes mellitus type I or II (irrespective of management)
    - Glycosylated haemoglobin (HbA1C) ≥ 8.0% (64 mmol/mol)
    - Fasting Plasma Glucose ≥ 7.0 mmol/L (126 mg/dL) (fasting is defined as no calorie intake for at least 8 hours)
    - For AZD5363 :
    - Diabetes mellitus type I
    - Fasting plasma glucose (fasting is defined as no calorific intake for at least 8 hours):
    - ≥ 7.0mmol/L (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus OR ≥ 9.3 mmol/L (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus
    - Glycosylated haemoglobin (HbA1C) ≥8.0% (64 mmol/mol)
    - Requirement for insulin for routine diabetic management and control
    - Requirement for more than two oral hypoglycaemic medications for routine diabetic management and control
14. Patients using drugs that are known potent inhibitors or potent inducers or substrates of cytochrome P450 are not eligible if those treatments cannot be substituted from 14 days prior to the first dose (except those for which the minimum wash-out period is longer, e.g Fluoxetine and Phenobarbital: 5 weeks, Rifabutin : 3 weeks and amiodarone: 27 weeks) and during the study
15. Patients using non-substitutable drugs, that are known to prolong QT interval or induce Torsades de Pointes, from 14 days prior to the first dose (except those for which the minimum wash-out period is longer) and during the study, are not eligible when they are supposed to be treated with vandetanib or AZD5363
16. Known clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis for patients likely to be treated with savolitinib.

    Patients with a past or resolved HBV infection are eligible if:
    - negative for HBsAg and positive for hepatitis B core antibody [anti-HBc] or
    - positive for HBsAg, but for > 6 months have had normal transaminases and HBV DNA levels between 0 – 2000 IU/ml (inactive carrier state) and willing to start and maintain antiviral treatment for

at least the duration of the study.

- HBV DNA levels >2000 IU/ml but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study

Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV RNA.

17. For patients likely to be treated with vistusertib, patients exposed to strong or moderate inhibitors or inducers of Pgp (MDR1) and BCRP are not eligible if those treatments cannot be substituted from 14 days prior to the first dose and during the study. Patients exposed to specific substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K are not eligible if those treatments cannot be substituted from a minimum of 5 x reported elimination half-life prior to the first dose and during the study
18. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug

SUBSTUDY 2: IMMUNOTHERAPY VERSUS MAINTENANCE THERAPY

INCLUSION CRITERIA :

1. Patients who received 4 cycles of an induction platinum-based chemotherapy and who are presenting a stable or a responding disease at the time of randomization
2. Patients who still meet the screening phase inclusion criteria and exclusion criteria excluding exclusion criteria 16.
3. Patients not eligible to substudy 1
4. EGFR and ALK status should be confirmed negative for all patients at this point
5. Patients will have had at least a 28-day washout period from the platinum-based regimen prior to randomization and should have recover (grade ≤1) from all residual toxicities, excluding alopecia.
6. Potentially reproductive patients must agree to use an effective contraceptive method (acceptable methods of contraception are described in section 9.1.1 and 10.1.1 of the protocol) while on treatment, beginning 2 weeks before the first dose of investigational product and for at least 4 months after the last dose of study drug. Male patients should refrain from fathering a child or donating sperm during the study and for at least 4 months following the last dose of study treatment.
7. Women of childbearing potential must have a negative serum pregnancy test done within 14 days of enrollment and/or urine pregnancy test 72 hours prior to the administration of the study drug.
8. Women who are breastfeeding should discontinue nursing prior to the first dose of study drug and until 4 months after the last dose.
9. Provision of signed and dated, written informed consent prior to randomization and to any study specific procedures, sampling and analysis.

EXCLUSION CRITERIA :

1. Life expectancy < 3 months.
2. Disease progression occurring at any time during chemotherapy and before randomization or toxicity that led to the discontinuation of the platinum-based chemotherapy before 4 full cycles have been delivered
3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab
4. Participation to another clinical study with an investigational product (IP) during the last 30 days
5. Toxicities of grade ≥2 from any previous anti-cancer therapy, with the exception of alopecia.
6. Altered haematopoietic or organ function, as indicated by the following criteria:
   - Polynuclear neutrophils < 1.5 x 10^9/L
   - Platelets < 100 x 10^9/L
   - Haemoglobin < 90 g/L
   - ALAT/ASAT > 2.5x ULN in the absence of or > 5x ULN in the presence of liver metastases
   - bilirubin > 1.5xULN. This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician

- serum creatinine clearance ≤40 mL/min (measured or calculated by Cockroft and Gault formula) or by 24-hour urine collection for determination of creatinine clearance

7. Mean resting QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 consecutive ECGs using Bazett's Correction
8. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent dose of other corticosteroid
9. Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded
10. Active or prior documented inflammatory disease (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion :
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone
11. History of primary immunodeficiency
12. History of allogeneic organ transplant
13. History of hypersensitivity to durvalumab or any excipient
14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, serious chronic gastrointestinal conditions associated with diarrhea, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B (patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg are eligible), hepatitis C (patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA) or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
15. Known history of previous clinical diagnosis of tuberculosis
16. History of leptomeningeal carcinomatosis
17. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab
18. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids
19. Subjects with uncontrolled seizures
20. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP (Note: Local surgery of isolated lesions for palliative intent is acceptable)

STUDY PROCEDURES:

After the patients have signed the informed consent form for the screening phase and all inclusion and exclusion criteria have been checked, eligible patients will be registered through the R&D Unicancer online e-CRF. An automatic reply, followed by an e-mail will confirm the success of the inclusion procedure and will deliver an inclusion number. The 5 digits number preceded by the letter L (for Lung) will identify the participating site on the first 2 digits followed by the position of the patient included (e.g L01003 for the third patient included in the site identified 01 in the SAFIR02 Lung study)
This number must be used as the unique patient identification (ID) number throughout the study especially for the identification of biological samples.
Once the site has received the patient ID, the biopsy can be performed to ensure that samples will be correctly identified. Inverting this sequence is not recommended as it may lead to a suboptimal procedure or to the misidentification of specimens (samples undergo more handling while they wait for getting the ID number, and the risk of error is increased).
If an archived frozen or FFPE sample, or a plasma sample is used, it must be first identified with the study patient ID number before being sent to the genomic platforms for DNA extraction and genomic analysis.

All the participating genomic platforms will perform :
-tumor DNA or ctDNA extractions
--Arrays CGH either with Affymetrix Cytoscan assays fresh tumor DNA or Affymetrix OncoScan chips for FFPE or ctDNA
-next generation sequencing with Ion Torrent PGM or Illumina MiSeq or MiniSeq, and AmpliSeq technology, using a panel of around 70 genes

Patients can be considered as pre-eligible for the targeted substudy 1 randomisation phase when both following mandatory conditions have been met : stable or responding disease has been observed after 4 cycles of chemotherapy (investigator judgment) and targetable alteration has been identified by the Molecular Tumor Board.

If not eligible for the substudy 1 randomisation phase, patients can be considered as pre-eligible for the immune substudy 2 randomization phase when both following mandatory conditions are met: stable or responding disease (investigator judgment) is observed after 4 cycles of a platinum-based chemotherapy AND not eligible to randomization in the substudy 1 (because patient had no targetable alteration identified by the Molecular Tumor Board, or failed to have a genomic profile for the tumor [low tumor cells percentage, technical issue during genomic analysis, etc.], or a non-inclusion criteria that precluded entry into the substudy 1).

Then the patients will have to sign a second substudy specific informed consent form for the randomization phase, in order to initiate all the selection and baseline assessments. The mandatory post-chemotherapy 28-day wash-out period following cycle 4 of chemotherapy will provide time to achieve all the required tests and examinations.

When all the criteria have been checked and are met, and after the mandatory wash out 28-day period has elapsed, login to the R&D Unicancer online e-CRF, click on the Patient ID link and proceed with the randomization. An automatic reply, followed by an e-mail will confirm the success of the randomization procedure. The randomization program will allocate the following treatments with a 2:1 ratio in favor of Arm A:

Substudy 1 : targeted therapies versus standard maintenance therapy

- Arm A1 / targeted arm: targeted maintenance from a list of targeted drugs (see Appendix 5) guided by the genomic analysis,

  or

- Arm B1 / standard arm : standard maintenance as per guidelines

Substudy 2 : immunotherapy versus standard maintenance therapy

- Arm A2 / immunotherapy maintenance arm: durvalumab or

  Arm B2 / standard arm : standard maintenance as per guidelines

Safety and efficacy assessments and visit schedule are described in the study flowchart.

D) DESCRIPTION OF STUDY DRUGS

Drug Name (IDN)	**Commercial Name**	**Pharmaceutical Form**	**Administration Route**	**Posology** (bd: twice daily, od: once daily)
Investigational therapies				
vistusertib	NA	tablet	per os	50 mg bd, continuous dosing
AZD4547	NA	tablet	per os	80 mg bd, 2 weeks on/1 week off
AZD5363	NA	tablets	per os	480 mg bd, 4 days on/3 days off
AZD8931	NA	tablet	per os	40 mg bd, continuous dosing
selumetinib	NA	capsule	per os	75 mg bd, continuous dosing
vandetanib	CAPRELSA®	tablet	per os	300 mg od, continuous dosing
Olaparib	LYNPARZA®	tablets	per os	300 mg bd continuous dosing
savolitinib	NA	tablets	per os	600 mg od continuous dosing (400 mg od for patient with body weight less than 50 kg)
Vemurafenib + Cobimetinib	Zelboraf®	tablets	per os	960 mg bd, continuous dosing
	Cotellic®	tablets	per os	60 mg od, 21 days on / 7 days off
Durvalumab	NA	Liquid formulation	Intra-venous	10 mg/kg, every 2 weeks
Standard maintenance treatments for non squamous NSCLC				
pemetrexed	ALIMTA®	powder for solution	Intra venous	500 mg/m^2, every 3 weeks
Standard maintenance treatments for squamous NSCLC				

Treatment is left to the investigator's decision as per local practice and shall be one of the 2 most common attitudes in France

1) Follow up with no active maintenance therapy

2) Gemcitabine

THERAPEUTIC SCHEME IN THE RANDOMIZED PHASE:

- Patients will be treated either with one of the investigational therapy or with maintenance treatment (pemetrexed for non squamous or standard practice for squamous)
- Cycles are defined in 28-day periods for vemurafenib+cobimetinib, in 14-day periods for durvalumab and in 21-day periods for all other investigational therapies
- Disease response will be assessed every 6 weeks (RECIST 1.1)
- Safety will be assessed continuously

TREATMENT DURATION

Treatment will be continued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment.

E) STATISTICAL ANALYSIS

SUBSTUDY 1 : Targeted therapies versus standard maintenance therapy

The primary objective of the SAFIR02 lung study is to demonstrate that targeted therapeutic approach in substudy 1 guided by the genomic analysis (arm A1) improves progression-free survival as compared to a non-targeted maintenance therapy (arm B1). The primary endpoint is progression-free survival. Assuming exponential survival, in order to detect an increase in median progression-free survival from 4 (arm B1) to 6 months (arm A1) (a hazard ratio of 0.66) with 80% power at a two-sided significance level of 0.05 using the logrank test and a 2:1 randomization (arm A1: arm B2), 205 events are required. Assuming a 72 months enrollment period with uniform accrual, and 12 months additional follow-up, a total of 230 patients needs to be randomized.

The primary analysis will be a Cox regression analysis, adjusted for the factors that were used as stratification variables in the randomization, to compare the progression-free survival between the two treatment arms. In an exploratory analysis, additional prognostic covariates (clinicopathological factors and genomic aberrations) will be added to the Cox proportional hazards regression models.

The Kaplan-Meier approach will be used to estimate survival rates for each treatment arm. The Cox proportional hazards model will be used to estimate the hazard ratio (HR) between the two treatment arms (ie, the magnitude of treatment effect) and its 95% confidence interval (CI).

Analysis of the efficacy criteria will be performed using the intent-to-treat (ITT) population, which is defined as the population of all randomized patients analyzed in the treatment group they were assigned to.

SUBSTUDY 2 : Immunotherapy versus standard maintenance therapy

The primary objective of the immune substudy 2 is to demonstrate that maintenance with immunotherapy (durvalumab, arm A2) improves progression-free survival as compared to a standard maintenance therapy (arm B2). The primary endpoint of the immune substudy 2 is also progression free survival. Assuming exponential survival, in order to detect an increase in median progression-free survival from 4 months (Arm B2: Standard) to 6.5 months (Arm A2: “Anti-PD-L1”), corresponding to a hazard ratio of 0.62, with 80% power at a two-sided significance level of 0.05 using the logrank test and a 2:1 randomization (arm A2: arm B2), 155 events are required. Assuming a 54 months enrolment period with uniform accrual, and an additional 5.5 months follow-up, a total of 180 patients need to be randomized.

The primary analysis will be a Cox regression analysis, adjusted for the factors that were used as stratification variables in the randomization, to compare the progression-free survival between the two treatment arms. The Kaplan-Meier approach will be used to estimate survival rates for each treatment arm. The Cox proportional hazards model will be used to estimate the hazard ratio (HR) between the two treatment arms (ie, the magnitude of treatment effect) and its 95% confidence interval (CI). Analysis of the efficacy criteria will be performed using the intent-to-treat (ITT) population, which is defined as the population of all randomized patients analyzed in the treatment group they were assigned to.

For the prospective pooled analysis of the SAFIR02 lung and SAFIR02 breast studies, a specific meta-analysis plan will be developed.

F) TRIAL DURATION
INCLUSION PERIOD: 6 YEARS
INTERVAL BETWEEN SCREENING AND RANDOMISATION: 4 MONTHS **ESTIMATED TREATMENT PERIOD:** 6 MONTHS **POST- TREATMENT FOLLOW-UP PERIOD :** 12 MONTHS IN SUBSTUDY 1, 24 MONTHS IN SUBSTUDY 2
OVERALL TRIAL DURATION : 8 YEARS

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1. ABBREVIATIONS

β-hCG	human chorionic gonadotrophin
AE	Adverse Event
ACE	Carcinoembryonic antigen
ADA	Antidrug antibody
ADL	Activities of Daily Living
ALAT (ALT)	Alanine aminotransferase
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALP	Alkalin phosphatase
ANC	Absolute neutrophil count
ANSM	Agence nationale de sécurité du médicament et des produits de santé
aPTT	Activated Partial thromboplastin Time
ASAT (AST)	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BD	Twice daily
BP	Blood pressure
BSA	Sinoatrial Block
BUN	Blood urea nitrogen
CI	Confidence Interval
CK	Creatinine kinase
CNG	Copy number gain
CNS	Central nervous system
CPP	Committee for Protection of Persons
CRA	Clinical Research Associate
CR	Complete response
CRF	Case report form
CT	Computerized tomography
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T-lymphocyte antigen
CYP	Cytochrome P450
dL	deciliter (100 ml)
DLCO	Diffusing Capacity for Carbon Monoxide (of the Lung)
DMB	Data monitoring board
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor, also known as ErbB1 or HER-1
ErbB1	EGFR, c-ErbB1; HER-1
ErbB2	c-ErbB2, also known as HER-2/neu
FFPE	Formalin fixed paraffin embedded
FISH/ CISH/SISH	Fluorescence in situ hybridization
FPG	Fasting Plasma Glucose
g	Grams
GCH array	Array comparative genomic hybridization
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
G-CSF, GM-CSF	Granulocyte-Colony Stimulating Factor, Granulocyte Macrophage-Colony Stimulating Factor
Hb	Hemoglobin
HDPE	High density polyethylene
HER2	Also known as HER-2/*neu* or c-ErbB2,
HGFR	Hepatocyte growth factor receptor
HPMC	Hydroxypropylmethylcellulose
HR	Hazard ratio
HR	Heart Rate
HRCT	Hight Resolution Computed Tomography
IB	Investigational brochure
IDMC	Independent data monitoring committee

IgG	Immunoglobulin G
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IM	Intramuscular
INR	International Normalized Ratio
irAE	Immune-related adverse event
ITT	Intent-to-treat
IV	Intravenous
L	Liter
LD	Longest diameter
LDH	Lactate dehydrogenase
LFT	Liver function tests
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
mg	Milligram(s)
mins	Minutes
mL	Milliliter(s)
MRI	Magnetic resonance imaging
MTB	Molecular tumor board
MTD	Maximum Tolerated Dose
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
nM	Nanomol
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
OD	Once daily
ORR	Objective response rate
OS	Overall Survival
ALP	Alkaline Phosphatase
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PgP	P-glycoprotein
PR	Partial response
PT	Prothrombin time
Q2W	Every two weeks
QTcF	Corrected QT by the Fridericia method
RECIST	Response Evaluation Criteria in Solid Tumors
RPED	Retinal Pigmented Epithelial Detachment
RPPA analysis	Reverse Phase Protein Array
SAE	Serious adverse event(s)
SC	Steering Committee
SD	Stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TT	Thrombin Time
TTP	Time to progression
ULN	Upper limit of normal

2. RATIONAL FOR THE TRIAL

2.1. Non-small cell lung cancer

With an incidence of 32,000 new cases per year in France, lung cancer is the second most common cancer in men and women. With a mortality rate of 28,000 cases, lung cancer is responsible for more deaths than breast cancer and colorectal cancer combined.
Ten to 15% of cases of lung cancer are of small-cell lung cancer and 85% are of non-small-cell lung cancer. The latter are normally subdivided into squamous-cell carcinomas, adenocarcinomas and large-cell cancers. The 5-year survival rate for NSCLC (including all stages) is 15%. This is due, in particular, to the incurability of the metastatic form of NSCLC, which represents about 65% of NSCLC cases at diagnosis.
NSCLC in its metastatic form has a median survival of 8 to 12 months in the absence of an EGFR-activating mutation or an ALK translocation. In the latter two cases, median survival is about 24 to 36 months (Soria et al., EGFR-mutated oncogene-addicted non-small cell lung cancer: Current trends and future prospects. Cancer Treatment Reviews 2012).
In all, this introduction underlines the need for new therapeutic strategies in metastatic non-small-cell lung cancer.

2.2. Targeted therapies in oncology

Targeted treatments have led to major advances in oncology. Some significant treatment targets have been identified in the last 10 years. Trastuzumab reduces the annual risk of relapse in patients with HER2+ breast cancer by 50% (Piccart, New England Journal of Medicine, 2005). Similarly, EGFR inhibitors have shown major efficacy in patients with lung cancer with EGFR mutation (Paez, Science, 2004). More recently, BRAF inhibitors have been associated with high response rates in patients with melanoma with BRAF mutation (Flaherty, New England Journal of Medicine, 2010). Interestingly, similarities are found between the significant targets: a) the involved genes are amplified or mutated and/or their expression modifies their phenotype, b) their expression results in oncogenic transformation, c) the genetic abberation appears prematurely in oncogenesis (Rosen N, IMPAKT meeting, 2009).
More recently, the molecular mechanisms mediating resistance to targeted therapies have been described. At least two families of different molecular mechanisms have been identified and could mediate the resistance of tumors to targeted therapies. The most frequently reported mechanism is related to the activation of an alternative pathway. As illustration, mutations of PI3KCA or K-Ras mediate resistance to trastuzumab and to cetuximab (Nagata, Cancer Cell, 2004, Lièvre, Cancer Res, 2006) by activating an intracellular kinase pathway.
The other mechanism of resistance involves the receptor itself. As illustration, the EGFR receptor may gain a secondary resistance (T790M), making it resistant to EGFR inhibitors (Soria et al., Cancer Treatment Reviews 2012). These resistance mechanisms may themselves be targeted in order to retrieve sensitivity to targeted therapy.
In total, several hundred targeted therapies are being developed in oncology, potentially generating several thousand combinations. It is predicted that each targeted therapy will be efficient in few patients, i.e., those with a genomic alteration of the target. In theory, identification of these targets in each patient could allow the administration of an efficient treatment, since the treatment would be based on the biological abnormalities present in the patient's tumor.

2.3. Non-small cell lung cancer: a large range of molecular abnormalities.

High throughput analysis have shown that NSCLC is a disease with a large number of genomic abnormalities resulting in cell proliferation, invasion, and inhibition of apoptosis. CGH array analysis have repeatedly shown that, in addition to amplifications of PI3K (33% of squamous-cell carcinomas and 6% of adenocarcinomas), EGFR (30%) and FGFR1 (22% of squamous-cell carcinomas), a substantial number of genes coding for kinases are amplified in 1 to 8% of patients. These high levels of amplifications mainly involve MET (8 to 21% of cases, depending on the series), HER2, AKT etc. (Perez-Moreno, CCR 2012). Also, high rates of PTEN deletion (30%) were found in patients with NSCLC.
More recently, high throughput sequencing analysis have demonstrated the existence of mutations in TP53, RB1, CDKN2A, and STK11, HER2, HER1, KRAS and NRAS but also in PI3K, PTEN, AKT1, MDM2, APC, KDR, MET, CTNNB1, ATM, BRAF and AKT1 (Perez-Moreno, CCR 2012).
In all, these findings show that a large number of molecular abnormalities could contribute to oncogenesis and to resistance to lung cancer treatments. Most abnormalities are found in only 2 to 10 % of patients and many molecular abnormalities may be observed in the tumor, and consequently the disease, of one patient only. Identification of these abnormalities in patients by high throughput analysis could permit more efficient treatment.

2.4. High throughput analysis for clinical practice.

In the SAFIR01 study, we were able to perform high throughput genome analysis in clinical research conditions (André, Lancet Oncology, 2014). Four hundred and twenty-three patients were enrolled in this study, and genome analysis were performed in 251 of them. A "targetable" abnormality was identified in 69% of these patients.
Following this study, several Ion Torrent PGM-type high throughput sequencing were developed in cancer centers, and data indicate that these sequencers are very reliable in detecting mutations. In a preliminary study, a 100% match was observed between a conventional (SANGER) and an Ion Torrent PGM sequencing technique (Lacroix, personal data).
In addition, trial IFCT0801 (TASTE) demonstrated the capacity of the Intergroupe Francophone de Cancérologie Thoracique [French lung cancer research group] to carry a national prospective trial including 152 patients in 25 recruiting centres with a systematic prescription based on the molecular analysis of resected NSCLC (EGFR and ERCC1).

2.5. Maintenance phase in lung cancer: a need for new drugs.

Patients with NSCLC generally receive four to six cycles of first-line metastatic chemotherapy. At the end of this treatment period, and in the absence of tumor progression, patients are either monitored until the tumor progression or included in a maintenance program (Edelman et al, JTO 2012). Switch maintenance therapy was shown to improve progression free survival in patients with NSCLC for Pemetrexed in the JMEN trial (Ciuleanu et al., Lancet 2009) and for Erlotinib in the SATURN trial (Cappuzo et al., 2010). Apart from the PARAMOUNT trial, which evaluates pemetrexed-based maintenance in non-squamous-cell NSCLC, the benefit of continuation maintenance therapy on survival of patients with NSCLC has not been shown. Maintenance is, however, considered a therapeutic option in the international guidelines (NCCN, ASCO and ESMO). Pemetrexed is the classical maintenance therapy in non-squamous patients, while erlotinib is the one in squamous patients. Median progression-free survival times under maintenance therapy are known to be short (for switch maintenance: SATURN trial Erlotinib 12,3 wks / Placebo 11,1 wks and JMEN trial Pemetrexed 4,3 months/ Placebo 2,6 months; for continuation maintenance : PARAMOUNT trial: Pemetrexed 4,1 months/ Placebo 2,8 months; AVAPERL NCT00762034 trial: Pemetrexed+Cisplatin+Bevacizumab then maintenance with Bevacizumab+Pemetrexed 7,4 months or Bevacizumab alone 3,7 months; POINTBREAK trial: Pemetrexed+Carboplatin+Bevacizumab followed by Pemetrexed+ Bevacizumab 6,0 months / Paclitaxel+Carboplatin+Bevacizumab followed by Bevacizumab 5,6 months).

The IUNO study (B025460), a randomized, double-blind, placebo-controlled, phase 3 maintenance erlotinib versus erlotinib initiated at the time of disease progression in patients with non EGFR mutated NSCLC, failed to show a benefit on overall survival or progression free survival in patients randomized to receive maintenance erlotinib compared to placebo.
Based on this results, since January 2016 erlotinib is no longer indicated for maintenance treatment in patients without an EGFR activating mutation.
Two randomized trials comparing gemcitabine maintenance versus best supportive care (BSC) provides the rational for the optional use of gemcitabine as a maintenance therapy in squamous-NSCLC (Brodowicz, 2006; Perol, 2012). In the first study, the median TTP throughout the study was significantly longer on the gemcitabine arm (6.6 months; 95% CI, 5.9–7.2 months) compared to the BSC arm (5.0 months; 95% CI, 4.5–5.7 months) (p < 0.001) and the median OS throughout the study was 13.0 months (95% CI, 11.0–16.7 months) on the gemciatbine arm, compared to 11.0 months (95% CI, 9.7–13.5 months) on the BSC arm (p = 0.195). In the second study, continuation maintenance with gemcitabine significantly prolonged PFS versus BSC (median PFS, 3.8 v 1.9 months; HR, 0.56; 95% CI, 0.44 to 0.72; log-rank P < .001) but this PFS benefit with gemcitabine continuation maintenance did not translate into a significant OS advantage versus observation alone (median OS, 12.1 v 10.8 months; HR, 0.89; 95% CI, 0.69 to 1.15; log-rank P = .3867); In both studies, ECOG PS0 patients seems to derived the largest benefit from gemcitabine maintenance. Accordingly, gemcitabine maintenance is considered as valid option as maintenance therapy by national guidelines (Cancer bronchique non à petites cellules - Référentiel national de RCP, INCa Mars 2015, available at www.ecancer.fr) and ESMO guidelines (Reck, 2014) consider that decisions about maintenance must take into account the histology, response to platinum-doublet chemotherapy, remaining toxicity after first-line chemotherapy, PS, and patient preference.

2.6. A targeted drug panel for a genomic-guided maintenance treatment

Molecular alterations in tumor cells have been critical to identify potential target and develop specific therapies. There are more and more targets described enabling physicians to deliver personalized treatment to the patients.

In NSCLC daily practice, patients are tested for EGFR mutation and/or ALK translocation to determine if they can benefit from respectively gefitinib/erlotinib and crizotinib treatments. There are some other targets identified and known as potentially of interest in lung cancer: Mammalian Target Of Rapamycin (mTOR), Fibroblast Growth Factor Receptor (FGFR), serine/threonine kinase AKT/protein kinase B (PKB), MEK, VEGFR, etc. There are already some drugs in development targeting that pathways and abnormalities.
We have identified specific targeted drugs we would like to test in this study. **All the information provided bellow are current at the time the initial protocol is written.** Pharmacology, safety, and efficacy updates for each drug will be available in the subsequent investigator Brochures.
The benefice-risk balance will be re-evaluated for each new IB version.

2.6.1. Vistusertib

Vistusertib is an inhibitor of the kinase activity of mammalian Target of Rapamycin (mTOR) serine threonine kinase, which plays a critical role in regulating cellular energy sensing, growth and metabolism. Deregulation of mTOR signalling is observed in many tumour types (Chiarini et al 2015; Xu et al 2014), and mutations or loss of function of upstream regulators such as TSC1/2, LKB1, or components of the phosphadidylinositol-3 kinase (PI3K) pathway such as PIK3CA, AKT or PTEN (phosphatase and tensin homolog deleted on chromosome ten) have been reported in most types of human tumours (Thorpe et al 2015; Martini et al 2014). The PI3K/AKT/mTOR cellular signalling pathway is summarised in Figure 1.

mTOR kinase forms two distinct multiprotein complexes called mTORC1 and mTORC2. The mTORC1 complex plays a key role in coupling nutrient sensing with the regulation of protein translation and cellular metabolism processes. It directly phosphorylates proteins such as p70S6K (S6K), (Magnuson et al 2012) and 4E-BP1 (Hsieh et al 2010), which are involved in controlling cellular growth and proliferation, as well as the sterol regulatory element binding protein (SREBP) (Bakan & Laplante 2012), a key modulator of metabolism and lipid synthesis. mTORC1 also phosphorylates a number of substrates which modulate autophagy and lysosome biogenesis (Betz & Hall 2013). mTORC2 has been reported to play a role in the cellular response to extra-cellular growth factors through largely unknown mechanisms. Its activation requires association with ribosomes and results in the phosphorylation of downstream targets such as the AGC family of protein kinases, which includes AKT, serumand glucocorticoid-induced kinases SGK and protein kinase C (PKC) (Su & Jacinto 2011).

Rapamycin and its analogues (rapalogues) are potent inhibitors of mTORC1 and have been shown to be clinically effective in certain cancer types such as endometrial cancer, mantle cell lymphoma, renal cell carcinoma (RCC) and breast cancer (Faivre et al 2006; Witzig et al 2005; Baselga et al 2012). Nevertheless, several resistance mechanisms have been shown to limit the response rate in clinical studies to rapamycin and analogues. There is evidence that inhibition of mTORC1 alone sets off a negative feedback mechanism that leads to increased AKT signalling. The elevation in AKT phosphorylation may at least in part explain the disappointing clinical results with rapamycin derivatives in many solid tumours.

Vistusertib is a selective inhibitor of mTOR kinases and inhibits signalling of both mTOR complexes, mTORC1 and mTORC2. Vistusertib is thereby molecularly differentiated from rapalogues:

- Vistusertib achieves more profound mTORC1 inhibition, in particular inhibiting phosphorylation of the rapamycin insensitive site on 4E-BP1 (T37/46). Vistusertib also inhibits mTORC2.
- Vistusertib has a broader range of growth inhibitory activity in vitro across tumour types compared to rapalogues. Vistusertib is especially effective in ER+ breast cancer cell lines and in in-vivo sensitive and resistant models to endocrine therapy.

As such, ATP-competitive dual TORC1/TORC2 inhibitors, like vistusertib, that inhibit both mTOR complexes may offer therapeutic advantages to rapalogues (Baselga et al 2012).

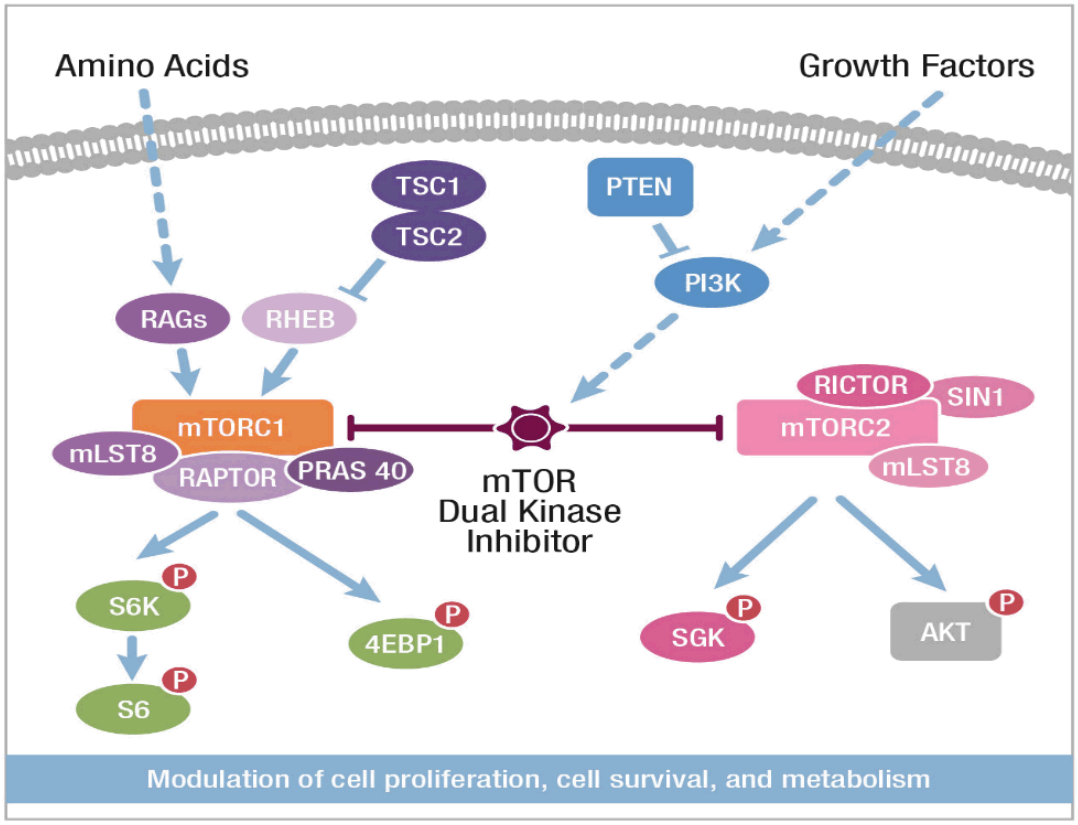


Figure 1: PI 3K/AKT/mTOR pathway
Simplified scheme of the mTOR signalling network. Signals from diverse extra- and intracellular cues (such as growth factors, stress, energy and nutrients) are sensed and integrated by the output of the two functionally distinct complexes — mammalian target of rapamycin complex 1 (mTORC1) and mTORC2 — to deliver a coordinated cellular response. AKT, protein kinase B; 4EBP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; PRAS40, proline-rich AKT substrate of 40 kDa; PTEN, phosphatase and tensin homologue; Rheb, Ras homolog enriched in brain; S6K, S6 kinase; TSC, tuberous sclerosis protein.

Clinical data are available from 3 Phase 1 and 1 Phase 2a AstraZeneca sponsored studies. These were designed to assess the safety, tolerability, PK and preliminary efficacy of vistusertib. There are also 10 ongoing externally sponsored studies. Safety and efficacy data are extensively described in the current IB.

2.6.2.AZD4547

AZD4547 is a potent and selective inhibitor of FGFR-1, 2 and 3 receptor tyrosine kinases (enzyme and cellular phosphorylation endpoints), and has a significantly lower potency for inhibition of IGF1R and KDR.

The FGFR family consists of four members each composed of an extracellular ligand binding domain, a trans-membrane domain and an intracellular cytoplasmic protein tyrosine kinase domain. Receptor activation leads to the recruitment and activation of specific downstream signalling partners that participate in the regulation of diverse process such as cell growth, cell metabolism and cell survival. Dysregulation of the FGFR pathway via genetic modifications of FGFR-1, 2, 3 or 4, including amplification, translocation, fusions and mutations have been described in a range of tumour types including breast cancer, gastric cancer, bladder cancer, lung cancer, endometrial cancer, cholangiocarcinoma and multiple myeloma. Non-clinical data indicate the presence of such modifications confer sensitivity to FGFR inhibitors. Inhibition of FGFR-mediated signalling can result in an anti-proliferative and/or pro-apoptotic activity, may have an anti-angiogenic effect, and may play a role in resistance to VEGF inhibitor therapy. Therefore AZD4547 may have the potential to provide clinical benefit in patients with a variety of advanced solid malignancies who have a FGFR-dependent mechanism.

Data presented at the American Association for Cancer Research and the American Society of Clinical Oncology (ASCO) in 2014 indicated clinical activity for FGFR inhibitors particularly in patients with FGFR3 mutations including the FGFR3-transforming acidic coiled-coil 3 translocation (Bahleda et al 2014, Dienstmann et al 2014, Sequist et al 2014). This presented an opportunity to explore disease areas with similar FGFR genetic aberrations with AZD4547.

The phase I studies D2610C00001 and D2610C00002 and phase II studies D2610C00003 and D2610C00004, are now reported and safety and efficacy data included in the current AZD4547 Investigator's Brochure.

2.6.3. AZD5363

AZD5363 is a potent, selective inhibitor of the kinase activity of the serine/threonine AKT/PKB that is being developed as a potential treatment for solid and haematological malignancies.

AKT is part of the AGC family of kinases (cAMP-dependent protein kinases A, cGMPdependent protein kinases G, and phospholipid-dependent protein kinases C). Mammalian cells express 3 closely related AKT isoforms: AKT1 (PKBá), AKT2 (PKBâ) and AKT3 (PKBã), all encoded by different genes. AKT is a node of multiple signalling pathways promoting tumorigenesis, inhibiting apoptosis, impacting on the cell cycle and promoting invasion and migration.

The phosphatidylinositol 3-kinase (PI3K)/AKT/phosphatase and tensin homologue (PTEN) pathway is frequently deregulated in cancer and drives tumour growth and cell survival (Lindsley 2010). All 3 AKT isoforms are activated in different tumour types including breast, prostate, ovarian, pancreatic and gastric cancers. This activation is often associated with resistance to established cancer therapies as well as advanced disease and/or poor prognosis (Altomare and Testa 2005). AKT activation in tumours is largely due to input from other signalling pathways upstream of AKT (eg, mutation of oncogenes such as Ras, Bcr-abl, mutation of receptor tyrosine kinases such as epithelial growth factor receptor, amplification of human epidermal growth factor receptor 2 (HER2), loss of PTEN function, mutations of PI3K).

Inhibitors of AKT are anticipated to have efficacy when dosed in combination with cytotoxic chemotherapies or in combination with targeted or antihormonal agents. AZD5363 inhibits all 3 AKT isoforms (AKT1, AKT2 and AKT3) and therefore has the potential to provide clinical benefit over a range of therapeutic indications.

Currently 5 AZ-sponsored Phase 1 and Phase 2 studies have been conducted or are ongoing for which safety and efficacy data are described in the current IB. In addition, 18 investigator sponsored studies are planned or have commenced recruitment. Only limited data from these studies were available for inclusion in the current IB.

2.6.4. AZD8931

AZD8931 is an oral, equipotent inhibitor against EGFR, erbB2 and erbB3, in development for the treatment of solid tumours.

The Epidermal Growth Factor Receptor (EGFR) family has been identified as a promising target for anti-cancer therapy. The EGFR family includes 4 members; EGFR/erbB1, erbB2/HER2, erbB3/HER3 and erbB4/HER4. Ligand binding to the EGFR, erbB3 and erbB4 receptors induces receptor homo- and hetero-dimerisation, leading to phosphorylation of critical sites in the tyrosine kinase domain, and subsequent activation of downstream pathways involved in cellular proliferation and survival (Olayioye et al 2000). ErbB2 is the preferred dimerisation partner for the other family members, and even though it has no ligand, it does become activated following dimerisation and erbB2-containing dimers exert the most potent mitogenic signal (Graus Porta et al 1997).

Aberrant EGFR and erbB2 activity has been identified in a number of human malignancies and is notable for its association with a more aggressive disease course and poor clinical outcome (Sjogren et al 1998; Nicholson et al 2001). In human tumours, activation occurs through receptor over-expression, autocrine growth factor loops, or the presence of activating mutations in the kinase domain (Voldborg et al 1997).

EGFR activation is seen in tumour types such as non-small cell lung cancer (NSCLC), breast, colorectal, and head and neck cancer. Over-expression of erbB2 is seen in a proportion of breast, ovarian, bladder, and gastric malignancies. Recent data suggests that simultaneous inhibition of EGFR, erbB2 and erbB3 may be of particular value in certain segments of breast cancer.

Therapeutic approaches to EGFR and/or erbB2 signalling modulation include the use of monoclonal antibodies targeting the extra-cellular domain (eg, trastuzumab and cetuximab) and small molecule EGFR tyrosine kinase (TK) inhibitors (eg, gefitinib and erlotinib). More recently, dual TKIs, with the ability to inhibit the tyrosine kinase

domain of both EGFR and erbB2, have been generated. The reversible dual TKI, lapatinib has shown activity in pre-treated patients (Burris et al 2005), and has been approved for use in combination with capecitabine for advanced metastatic breast cancer that is HER2 positive.

AZD8931 is being developed with the expectation that, as an inhibitor of both EGFR and erbB2 receptor kinases, it will provide superior efficacy compared to currently available inhibitors of either target alone.

AZD8931 is currently engaged in a development program that comprises completed and ongoing phase I studies and ongoing phase II studies (advanced solid malignancies, breast cancer, gastric cancer). Reported dose limiting toxicities were diarrhoea, rash, keratitis, oesophagitis. AZD8931 40mg bd has been determined as the clinically feasible and optimum dose to be suitable for potential long term treatment. This dose has an acceptable safety and tolerability profile based on phase I clinical studies. The potential for adverse drug reactions associated with AZD8931 are based on the adverse event profile of the class of drugs that inhibit the EGFR and/ or erbB2 signalling pathways, and from observations from non-clinical and clinical studies of AZD8931. The emerging profile lists the following adverse events : diarrhoea, stomatitis, rashes, dry eye / conjunctivitis, dry skin.

The phase II THYME study evaluated AZD8931/placebo in combination with weekly paclitaxel in patients with low HER2- expressing locally recurrent and /or metastatic breast cancer. A statistically significant higher response rate was seen for AZD8931 (59%) compared with placebo (41%). However, the study failed to show a therapeutic benefit in terms of PFS (primary objective) and OS.

The phase II MINT study evaluated AZD8931/placebo in combination with anastrozole in patients with hormone receptor positive, endocrine therapy naive, locally advanced or metastatic breast cancer. The trial was prematurely stopped due to the lack of benefit observed in the overall population.

Therefore, as of 9th November 2012, AstraZeneca has made the decision to discontinue AstraZeneca sponsored development of AZD8931.

As a consequence, the production of AZD8931 has been interrupted by AstraZeneca, as well as the supply of new batches. Due to the depletion of stocks, no new orientation to this targeted therapy will be made from 1rst April 2017.

2.6.5.Selumetinib

Selumetinib (AZD6244, ARRY-142886) is a potent, selective, allosteric inhibitor of MEK that is non-competitive with respect to ATP, licensed for development by AZ Pharmaceuticals from Array BioPharma, and currently in Phase III development for oncology indications.

In cancer cells, signalling through the RAS/RAF/MEK/ERK pathway is frequently disregulated due to enhanced mitogenic stimulation at the level of growth factor receptors or activating mutations in RAS or RAF oncogenes. Inhibition of MEK, which lies downstream from these over-activated targets blocks inappropriate signal transduction in the pathway and is anticipated to arrest cancer cell proliferation and growth, offering a promising anti-cancer therapeutic strategy.

Although it has been hypothesised that benefit from MEK inhibition may primarily occur in patients with RAS- or RAF-mutation positive tumours, emerging information suggests that patients with tumours that do not have these mutations may also benefit from treatment. Clinical testing of selumetinib efficacy has focused on RAS- or RAF-driven cancers.

Non-clinical development

Selumetinib has been shown to inhibit growth and/or the survival of selected tumour cell lines in vitro and xenograft growth in vivo either as monotherapy or in combination with established chemotherapies, including docetaxel. Selumetinib has been shown to be particularly potent in inhibiting growth in cell lines with activating BRAF and KRAS gene mutations. Selumetinib has an acceptable pharmacological/toxicological profile for administration to patients with advanced cancer and healthy male volunteers receiving limited exposure to selumetinib in clinical pharmacology studies.

Clinical development

Initial clinical studies used an oral suspension of selumetinib free-base prepared as an aqueous solution of SBE-CD (Captisol®), referred to as the selumetinib free-base suspension formulation. Objective responses to selumetinib monotherapy have been demonstrated using the free-base suspension formulation in patients with

NSCLC, melanoma and pancreatic cancer, however, the observed clinical activity was similar to that of the comparator chemotherapy agents used in these randomised open-label studies.

Subsequent studies of selumetinib have been conducted using the Hyd-Sulfate capsule formulation. Second-line treatment with selumetinib in combination with docetaxel, for locally advanced or metastatic NSCLC (Stage IIIB to IV) in patients with KRAS mutation-positive tumours, was suggestive of clinical benefit in a randomised Phase II study (Study D1532C00016); however, SELECT-2 (Phase II) conducted in patients with KRAS wild-type NSCLC, and SELECT-1 (Phase III), in patients with KRAS mutation-positive NSCLC, did not show a significant improvement in OS, PFS or response rate.

Data from a Phase II randomised open-label investigator-sponsored study has demonstrated clinical activity of selumetinib monotherapy in patients with metastatic uveal melanoma (Carvajal et al 2014). Median PFS, OS and response rates appeared higher in patients treated with selumetinib than in those receiving temozolomide or dacarbazine. These data led to initiation of a randomised double-blind Phase III study of selumetinib in combination with dacarbazine versus placebo plus dacarbazine in patients with metastatic uveal melanoma not previously treated with systemic therapy (SUMIT study; completed). However, analysis of the primary endpoint, PFS according to a blinded independent central review, demonstrated no statisticially significant or clinically meaningful benefit for selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine.

Data from an investigator-sponsored pilot study in patients, with recurrent or metastatic differentiated thyroid cancer, have demonstrated reacquisition of radiaoactive iodine (RAI) uptake in previously refractory lesions, and increased RAI uptake in partially avid lesions, after pre-treatment with selumetinib (Ho et al 2013). Reduction in tumour size has also been demonstrated in patients re-treated with RAI. This evidence of clinical benefit led to initiation of a Phase III study of selumetinib with adjuvant RAI in patients with differentiated thyroid cancer (D1532C00065; ASTRA; ongoing).

2.6.6. Vandetanib

Vandetanib (CAPRELSA™, also previously known as ZACTIMA™, ZD6474) is a potent inhibitor of the tyrosine kinase activity of vascular endothelial growth factor receptor (VEGFR; also known as kinase insert domain containing receptor)-2, an endothelial cell receptor for vascular endothelial growth factor (VEGF), and also possesses activity against epidermal growth factor receptor (EGFR) and Rearranged during Transfection (RET) tyrosine kinases. VEGF is a key mediator of endothelial cell proliferation, and the initiation of new blood vessel growth. This process, termed angiogenesis, is essential for the growth and dissemination of tumours. By targeting both angiogenesis and EGFR- and RET-dependent tumour cell growth, it is hoped that the growth of tumours will be controlled, with relative sparing of normal tissues.

AstraZeneca has completed one Phase I/II study (Study D4200C00098), two Phase II studies (Studies D4200C00008 and D4200C00068), one Phase III study (Study D4200C00058) and one Phase IV study (Study D4200C00097; Parts A and B) in patients with advanced medullary thyroid cancer (MTC). Study D4200C00058 demonstrated a statistically significant improvement in progression-free survival (PFS), which was supported by a high response rate and a long response duration for vandetanib compared with placebo. The starting dose was 300 mg/day of vandetanib, which is the maximum tolerated dose. No statistically significant difference was seen between vandetanib and placebo in overall survival (OS), based on both the primary analysis and the final OS analysis; note, Study D4200C00058 allowed cross over to vandetanib treatment upon progression. The major side effects of vandetanib are diarrhoea, fatigue, hypertension, nausea and rash; in addition, vandetanib is associated with prolongation of the QT interval. During Study D4200C00058, patients were able to remain on vandetanib for a long duration (median: 1 year 9 months) through the use of standard medical therapy and dose reduction, to manage the toxicity associated with vandetanib. Vandetanib has received marketing approval in over 40 countries worldwide for the treatment of MTC in adult patients with locally advanced or metastatic disease. Furthermore, in MTC, Study D4200C00088 has been completed; this study randomised patients with MTC to vandetanib 300 mg daily versus vandetanib 300 mg daily with a patient outreach programme. Study D4200C00088 did not meet its primary endpoint of reduction in Grade 2 reported events in the patient outreach arm. The reported safety profile was similar across both arms and was consistent with the known safety profile for vandetanib. AstraZeneca has also completed Parts A and B of a double-blind, randomized Phase IV study (Study D4200C00097) in patients with advanced MTC. The study is based on a post-approval commitment to evaluate safety and efficacy at 2 starting doses of vandetanib (150 and 300 mg/day). Although the frequency and severity of adverse events (AEs) in Part A were higher in the 300 mg cohort, they were consistent with previously observed toxicity across the vandetanib development programme and no new findings were reported. More responses were observed in the 300 mg cohort and more progressive disease was observed in the 150 mg cohort. However, due to the small sample size, there was no statistical power to detect any true difference

between the treatment groups; therefore, the results can be considered as descriptive. In Part B, too few patients received vandetanib 100 mg, 150 mg or 200 mg to make any safety conclusions; however, the AE profile in the vandetanib 300 mg group was generally consistent with that reported in Part A. In addition, Study D4200C00098 demonstrated the safety and tolerability of vandetanib in Japanese patients with MTC.

In addition to MTC, vandetanib was evaluated in four Phase III studies in patients with advanced non-small cell lung cancer (NSCLC). Two studies investigated vandetanib in combination with chemotherapy (Study D4200C00032 with docetaxel and Study D4200C00036 with pemetrexed), and 2 studies investigated vandetanib as monotherapy (Study D4200C00057 compared to erlotinib and Study D4200C00044 compared to best supportive care [BSC] in patients who have previously received an EGFR inhibitor). The addition of vandetanib to docetaxel provided a statistically significant advantage in PFS compared with docetaxel alone; in the smaller study with pemetrexed, there was a positive trend for PFS in favour of the addition of vandetanib. Study D4200C00057 did not meet the goal of demonstrating superiority in PFS compared with erlotinib, but the efficacy of the 2 drugs was similar. Likewise, Study D4200C00044 did not demonstrate superiority of vandetanib in OS compared to BSC alone; efficacy of vandetanib in combination with BSC was shown to be similar to placebo in combination with BSC.

Vandetanib was also evaluated in a Phase II study in patients with differentiated thyroid cancer (DTC; papillary or follicular thyroid carcinoma) failing or unsuitable for radioiodine therapy, Study D4200C00079 (Leboulleux et al 2012); this was a randomised, double-blind study comparing 300 mg daily vandetanib versus placebo. A significant PFS advantage was seen in the vandetanib-treated patients compared with placebo-treated patients (median PFS: 11 months versus 5.8 months; hazard ratio [HR] 0.63; 95% confidence interval [CI]: 0.43, 0.92). While not statistically significant, 3-year OS data showed a numerical advantage in favour of vandetanib (59% versus 49%). The AEs reported in this study were similar to those reported previously across the vandetanib monotherapy programme.

2.6.7. Olaparib

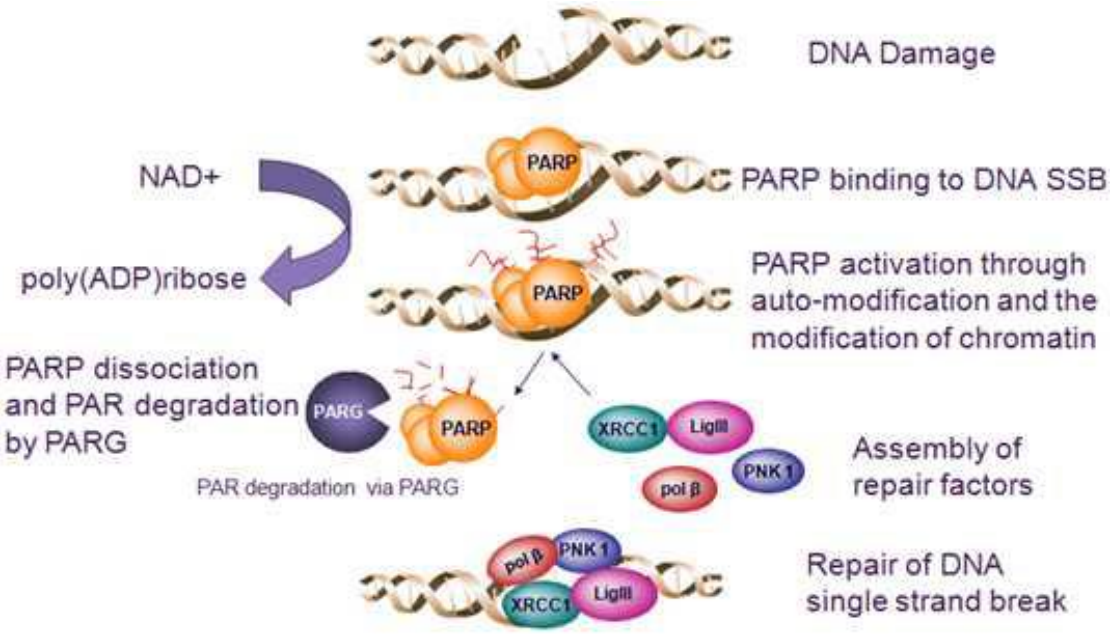
Olaparib (AZD2281, KU-0059436) is a potent inhibitor of PARP developed as a monotherapy as well as for combination with chemotherapy, ionising radiation and other anti-cancer agents including novel agents and immunotherapy. The approved tradename for olaparib is LYNPARZA.

PARP inhibition is a novel approach to targeting tumours that have HRD. In HRD tumours, single agent treatment with olaparib can lead to tumour regression by a process known as synthetic lethality; a result of the accumulation of un-repaired deoxyribonucleic acid (DNA) double-strand breaks (DSBs) and an unsupportable increase in genomic instability. Olaparib may also enhance the DNA damaging effects of chemotherapy and ionising radiation. Within the clinical development programme the intention is to assess tolerability and efficacy of olaparib in patients with advanced solid tumours enriched for HRD, including BRCA mutated cancers. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared to currently available chemotherapy regimens.

There are 17 known members of the PARP family of proteins (Hottiger et al 2010) and olaparib has been demonstrated to have low nM potency against PARP-1, PARP-2 and PARP-3. Only PARP-1 and PARP-2 are associated with the repair of DNA single strand breaks (SSBs) and while PARP-1 is the main family member involved in the repair of DNA SSBs, PARP-2 still has the ability to bind to DNA and compensate for PARP-1 activity in this regard. PARP-1 has also been implicated in the repair of DNA DSBs and this activity has recently been proposed to contribute directly to the mechanism of action of PARP-1 inhibitors (Ceccaldi et al 2015, Mateos-Gomez et al 2015). PARP-2 has been shown to play an essential role in hematopoietic stem/progenitor cell survival under steady-state conditions and in response to stress (Farrés et al, 2013). PARP-3 does not have a known role in DNA SSB repair but rather accelerates DNA DSB repair through non-homologous end joining (Rulten et al 2011). Recent data, however, suggest that PARP-3 inhibition does not contribute towards anti-tumour activity against BRCA mutated cancers, since a follow-on PARP inhibitor (AZD2461) that does not inhibit PARP-3 is still effective at causing BRCA mutated tumour regression in preclinical models (Jaspers et al 2013).

Studies on how PARP-1 modulates DNA repair, and other processes, have identified the importance of the formation of PAR chains within the nucleus (Althaus and Richter 1987). The DNA-bound, activated PARP-1 utilizes nicotinamide adenine dinucleotide (NAD+) to synthesize long polymer chains (PAR) on a variety of nuclear target proteins, including topoisomerases, histones and PARP-1 itself (Figure 2).

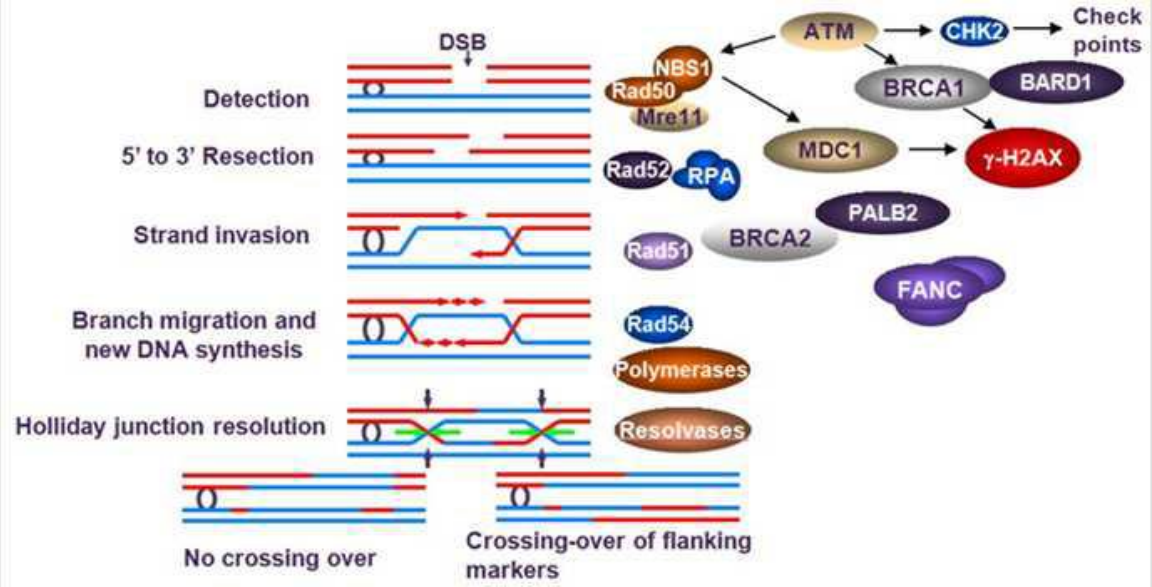
Figure 2: The role of PARP-1 in DNA single strand break repair



BRCA1 and BRCA2 defective tumours have been demonstrated to be intrinsically sensitive to PARP inhibitors, both pre-clinically in BRCA-deficient cells (Farmer et al 2005) and in BRCA mutated tumour in vivo models (Rottenberg et al 2008, Hay et al 2009, Kortmann et al 2010) and in the clinic (Fong et al 2009). BRCA1 and BRCA2 are human genes that belong to a class known as tumour suppressors. In normal cells, BRCA1 and BRCA2 help ensure the stability of the cell's genetic material (DNA) and help prevent cancer formation (Miki et al 1994, Wooster et al 1995). Both BRCA1 and BRCA2 proteins are critical for the repair of DNA DSBs by homologous recombination (Gudmundsdottir and Ashworth 2006). Loss of function of BRCA1 or BRCA2 results in increased mutation and genome instability (Venkitaraman 2002). It is this increased genomic instability that is thought to be responsible for the significantly increased cancer risk of patients with gBRCA mutations. However, the lack of functional BRCA1 or BRCA2 in tumours also represents an opportunity for targeted treatment with PARP inhibitors.

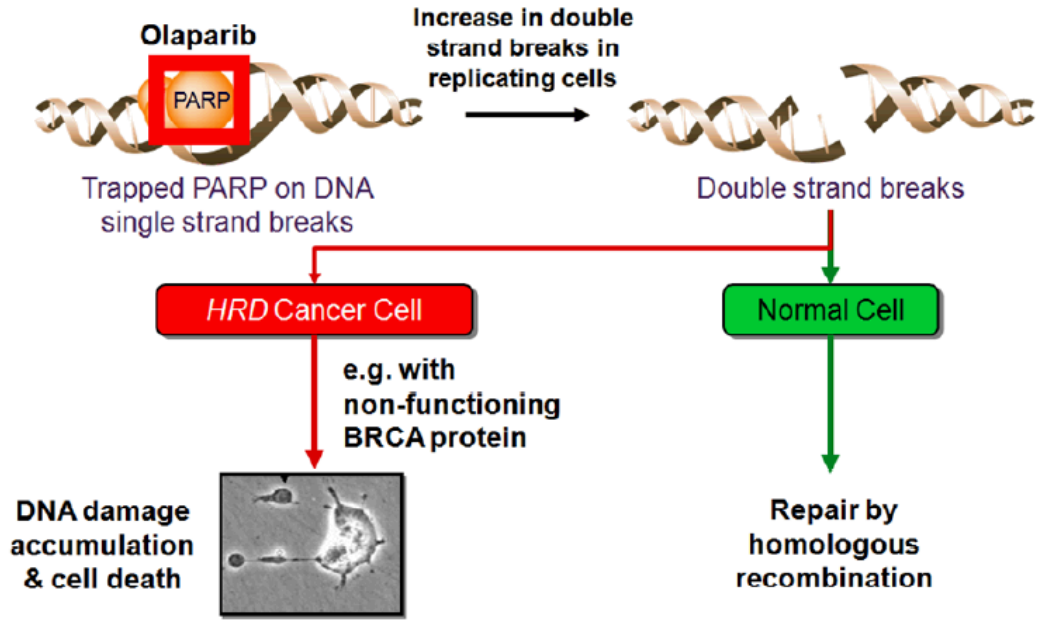
The mechanism of action for olaparib activity as a single agent has been proposed to involve the trapping of inactivated PARP onto the single-strand breaks preventing their repair and generating a potential block for cellular DNA replication (Helleday 2011, Murai et al 2012). An important consequence of this is that processing of trapped PARP-DNA complexes and/or the stalling of replication forks, or collapsing of replication forks, is predicted to lead to the generation of the more serious DNA DSBs (Helleday 2011, Murai et al 2012). These DSBs would normally be repaired by a process that involves ATM (a major DNA DSB signaling kinase, the 'MRN' nuclease protein complex; made up of Meiotic Recombination 11 Homolog A [MRE11A], human RAD50 homolog (RAD50) and Nijmegen breakage syndrome1 [NBS1]) and additional homologous recombination DNA repair (HRR) proteins such as human RAD51 (E. coli) homolog gene (RAD51), PALB2, BRCA1 and BRCA2 depicted in Figure 3.

Figure 3: Repair of DNA double strand breaks (DSBs) by HRR



In tumours with HRD, such as those with BRCA mutations, single agent treatment with olaparib can lead to cell kill and tumour regressions by a process known as synthetic lethality where neither the deficiency in HRR nor PARP inhibition alone is cytotoxic but where the combination of the 2 leads to cell death (Figure 4).

Figure 4: Single agent activity of olaparib in HRD tumours



In some instances where DNA repair defects may not result in the same level of sensitivity as BRCA mutations, and therefore single agent olaparib treatment may not be sufficient to induce cell kill through synthetic lethality, it may still be possible to induce tumour cell death through combinations with ionising radiation or chemotherapies that either increase DNA damage accumulation or mitotic stress. The latter is relevant since it is often during mitosis that unrepaired DNA damage leads to cell death through a process known as mitotic catastrophe (Castedo et al 2004) and mitotic spindle poisons such as taxanes increase the likelihood of mitotic catastrophe occurring.

Non-clinical studies looking at combinations of olaparib with chemotherapies such as alkylating agents, topoisomerase I inhibitors, platinum agents and taxanes, have demonstrated increased efficacy that ranges from additive to synergistic. For example, PARP inhibitors have been used to show that attenuating PARP activity leads to the chemopotentiation of temozolomide (TMZ), topotecan, irinotecan and cisplatin cytotoxicity in both in vitro and in vivo models (Delaney et al 2000, Evers et al 2008, Menear et al 2008, Miknyoczki et al 2003,

Rottenberg et al 2008, Hay et al 2009). Olaparib has also been shown to potentiate ionizing radiation in preclinical lung cancer models (Senra et al 2011).

Therefore, there are at least 2 potential ways in which PARP inhibitors such as olaparib can be used to induce tumour cell death, namely as a single agent or in combination with ionizing radiation or chemotherapy.

Most high-grade serous ovarian cancers have abnormalities of BRCA1 or BRCA2 (germline or somatic mutations, or in the case of BRCA1, promoter methylation and loss of expression) (Gilks and Prat 2009; Kobel et al 2008). A first-in-man Phase I dose escalation trial of single agent olaparib in patients enriched with hereditary gBRCA mutations has indicated substantial PARP inhibition in surrogate tissues and anti-tumour activity in 9/15 (60%) ovarian cancer patients with hereditary BRCA mutations, based on combined Response Evaluation Criteria in Solid Tumours (RECIST) and Gynaecological Cancer Intergroup CA-125 criteria (Fong et al 2009), while additional trials (Tutt et al 2010; Audeh et al 2010) in gBRCA mutated breast and ovarian cancer patients extended these findings. Further clinical studies suggest single agent olaparib activity in BRCA mutated prostate and pancreas cancers (Mateo et al 2015, Kaufman et al 2015).

PARP inhibition with olaparib is expected to have significantly reduced effects on normal cells that are wild-type or heterozygous for both BRCA1 and BRCA2 (Farmer et al 2005) and HRR. In patients with gBRCA mutations, their normal tissues will carry only one mutated copy of the relevant BRCA gene, but their tumours are expected to have lost both functional copies. This is important for the selective therapeutic window of olaparib (ie, effect on the tumour versus the effect on normal tissue) and leads to an acceptable tolerability profile for long term clinical use in a clearly identifiable and targeted patient population most likely to derive benefit.

There is also evidence that PARP inhibition can be an effective option for platinum-sensitive tumours, such as ovarian cancer. Platinum agents also induce DNA adducts where either their processing or impact on replication forks results in DNA double strand breaks that require HRR for effective and accurate repair. As with PARP inhibition, HRD results in a high degree of platinum sensitivity in ovarian cancer (Bowtell 2010). Moreover, preclinical data show that sensitivity to platinum agents correlates with sensitivity to olaparib in ovarian cancer cell lines, as well as in cell lines derived from other tumour types where platinum is standard of care (Mason et al 2012). Consistent with this are the clinical study data that demonstrate a greater response to olaparib in platinum responders (Fong et al 2010). Long term treatment with platinum agents is associated with significant toxicity whereas olaparib is a well tolerated and effective treatment for the maintenance setting which can be targeted to patients who are most likely to receive benefit, ie, platinum responsive ovarian cancer patients with tumours harbouring a BRCA mutation (Ledermann et al 2012).

It is the molecular targeting of olaparib to specific subsets of tumours that has raised the opportunity for a relatively non-toxic cancer monotherapy using olaparib (Ashworth 2008, O'Connor et al 2007). Pre-clinically, PARP inhibitors display anti-tumour activity to a variety of tumour cell lines. This sensitivity has been shown to involve deficiencies in components of HRR, such as the RAD51, Fanconia anaemia, and the ataxia telangiectasia and Rad3-related (ATR) genes, as well as in other DNA DSB repair factors such as the MRE11A, its complex partners - NBS1 and RAD50, and the ATM gene that regulates this 'MRN' complex (McCabe et al 2006). In the case of ATM, inactivating mutations/deletions have been shown to correlate with olaparib sensitivity in preclinical models of haematological malignancies such as chronic lymphocytic leukaemia and mantle cell lymphoma in which are both associated with deletions of chromosome 11q 22-23 where the ATM gene resides (Williamson et al 2010; Weston et al 2010). In a clinical study of patients with metastatic prostate cancer and deleterious mutations or deletions of the ATM gene, olaparib was associated with single agent clinical responses (Mateo et al 2015). Preclinical data further demonstrated a correlation of olaparib sensitivity with low ATM protein expression in gastric cancer cell lines. This, coupled with evidence of low or nondetectable ATM protein expression in ~15% of clinical gastric cancer samples has led to a randomized Phase II gastric cancer trial assessing the clinical response of patients with tumours differing in their ATM status (Bang et al 2013) and a subsequent Phase III trial in gastric cancer (Study D081BC00004).

As for BRCA1 and BRCA2, many other proteins involved in the homologous recombination repair mecanisms are now recognized to also contribute to hereditary cancer risk including ATM, RAD51C, RAD51D and PALB2 (Renwick et al, 2006; Rahman and al, 2007; Meindl and al, 2010). Therefore, targeting ATM, RAD51C, RAD51D and PALB2 alterations with olaparib could be of interest.

2.6.8.Savolitinib

Savolitinib (AZD6094) is a potent and selective small molecule MET kinase inhibitor with significant antitumour activity in development for the treatment of patients with cancer.

Mesenchymal epithelial transition (MET) receptor, also known as c-Met, is a transmembrane receptor essential for embryonic development and wound healing, and is normally activated through interaction with its specific ligand hepatocyte growth factor (HGF). The MET receptor is deregulated in many types of human malignancies, including cancers of the kidney, liver, stomach, lung, breast and brain. Aberrant activation of the HGF/MET axis in tumours triggers tumour growth, promotes tumour angiogenesis and induces tumour metastasis. In addition, abnormal MET activation is associated with drug resistance and is correlated with poor prognosis (Ishibe et al 2009; Lai et al 2009, Park et al 2012, Schmidt et al 1997). Recently, MET has become an important target of intensive research in search of specific inhibitors as potential new therapies for cancers driven by MET activation

Current MET inhibitors in the clinic fall into 2 main classes: monoclonal antibodies and small molecule kinase inhibitors. Antibodies predominantly target the HGF receptor MET, with a few targeting the circulating ligand HGF. The majority of MET kinase inhibitors target multiple kinases, with only a few selective MET kinase inhibitors. A multi-targeted MET inhibitor (cabozantinib) has been approved by the Food and Drug Administration (FDA) for the treatment of metastatic medullary thyroid carcinoma; however, it is thought that its activity in this patient population may be related to Rearranged during Transfection inhibition in addition to the inhibition of MET (Elisei et al 2013). Results from clinical trials of MET inhibitors in combination with other targeted therapies are also promising (Mok et al 2012, Oliner et al 2012; Spigel et al 2011). However, more studies are needed to determine the efficacy of MET targeting with a single agent.

Non-clinical development

In nonclinical studies, savolitinib demonstrated strong in vitro and in vivo activity against MET kinase and its downstream signalling targets and inhibited tumour cell growth. In particular, the potency of savolitinib on TGI was related to target status. Tumours driven by MET (such as gastric cancer and lung cancer with MET gene amplification, and glioblastoma with a HGF autocrine loop) were highly sensitive to savolitinib. The effect of savolitinib on tumours with MET overexpression has not yet been fully characterised. For tumours in which activation of multiple pathways are present (eg, the NSCLC cell NCI-H441 in which both MET and EGFR are overexpressed) a combination of savolitinib with the EGFR inhibitor erlotinib produced much greater efficacy than either compound alone.

The toxicity of savolitinib has been well characterised in general toxicology studies in rats and dogs and information from genetic toxicology and reproductive toxicology studies is also available. The principal finding following repeat dosing was the effect on the lymphoreticular system, which included decreased cellularity in lymphoid tissues. There were also effects on the GI tract. After 13 weeks of dosing, in addition to GI and lymphoreticular changes, effects were seen in the liver (including centrilobular degeneration and vacuolation) and adrenals (cortical hypertrophy). In rats only, there were noteworthy effects in kidney, urinary bladder and urinary tract (including tubular basophilia and urothelial hyperplasia), thyroid (follicular hypertrophy) and heart (chronic progressive cardiomyopathy). There were also effects on male and female reproductive tracts. Savolitinib showed adverse effects on female reproduction in rats.In dogs, there was evidence of testicular toxicity.

Clinical development

Savolitinib is currently in Phase I/II of clinical development. It should be noted that efficacy data from ongoing studies are preliminary, unvalidated and subject to change. Efficacy data are available from Phase I and Phase II studies based on a data cut-off date of 27 February 2017.

- In the Phase I monotherapy study on advanced solid tumors, D5081C00001, there were 48 patients in the All Subjects population, and of these,3 patients experienced a partial response and a fourth patient with PRCC received benefit as evidenced by a 25% decrease in tumour measurements from baseline. All 4 patients had MET alterations in their tumours.

In the Phase II monotherapy studyon papillary renal cell carcinoma (PRCC), D5082C00002, 109 patients dosed with savolitinib. 8 of 44 (18.2%) c-MET positive patients achieved a partial response; all of these responses are in patients with confirmed MET alterations.

In summary, savolitinib has shown promising efficacy in patients with tumour MET alterations. In general, savolitinib is well tolerated but requires close attention to monitoring of hepatic function (similar to other tyrosine kinase inhibitors [TKIs]).

Savolitinib has the potential to address major unmet medical needs in c-Met-driven subsets of Non-Small Cell Lung Cancer (NSCLC), a disease that is estimated to afflict approximately 1.7 million new patients annually worldwide.

Savolitinib continues to be explored in a range of MET-driven NSCLC settings including:

-Savolitinib in combination with Tagrisso or Iressa in Phase Ib expansions of ongoing studies in advanced EGFR mutant NSCLC who progressed on previous EGFR TKIs.

-Savolitinib + Tagrisso combination Phase Ib study in third-line NSCLC (for patients progressing on T790M-directed therapies)

-Savolitinib monotherapy Phase II study in NSCLC and PSC (Pulmonary sarcomatoid carcinoma).

2.6.9. Vemurafenib (Zelboraf®) + cobimetinib (Cotellic®)

Vemurafenib is an oral BRAF inhibitor that specifically targets the V600E isoform (Flaherty and al., 2010; Heakal and al, 2011).

One of the established signaling pathways in cancer development is the mitogen-activated protein kinase (MAPK) pathway. This pathway links extracellular stimuli, such as growth factors and hormone, to gene expression in the nucleus. Growth factor signals progress through the proteins RAS, BRAF, MEK and ERK, leading to cell proliferation. Mutations in the BRAF gene cause elevated kinase activity of the BRAF protein, which is seen in 8% of all solid tumors and in 50% of melanoma cases. The BRAF V600E mutation (rs113488022), which involves the substitution of valine (V) by glutamate (E) within the activation segment of the kinase domain , represents the vast majority of all BRAF mutations in cancer.

The RAF family is a set of serine/threonine kinases, which include BRAF, ARAF and CRAF (also called RAF1), that signals through phosphorylation of other downstream kinases. Upstream from RAF is RAS, the guanine nucleotide-binding protein activated by the binding of GTP. In the normal signaling pathway, an extracellular signal binds to a receptor tyrosine kinase on the cell surface. The types of receptors that signal through tyrosine kinases include those for fibroblast growth factors (FGFR), plate-derived growth factors (PDGFR), vascular epidermal growth factors (VEGFR), epidermal growth factors (EGFR), and nerve growth factors (NGFR), among others. When bound to the ligand, the receptor tyrosine kinase undergoes autophosphorylation of its tyrosine residues. This results in the phosphorylation of GRB2, an adapter protein that binds to the guanine nucleotide exchange factor, SOS. The GRB2/SOS complex stimulates inactive RAS by replacing bound GDP with GTP. Activated RAS causes BRAF to form a dimer with the other RAF isoforms ARAF and CRAF. Dimerization activates and phosphorylates MEK, which is a dual-specificity tyrosine and serine/threonine kinase. The main downstream target of MEK is ERK (also called MAPK). Upon phosphorylation by MEK, ERK can directly phosphorylate and activate a variety of transcription factors, such as Ets-1, c-Jun and c-Myc.

In mutated BRAF, the protein does not form dimers with the other RAF isoforms. The resulting monomer signals down the pathway regardless of any extracellular growth stimuli or RAS activity, resulting in elevated growth activity. The V600E isoform results in a structural conformation change that makes the ATP binding site constantly accessible.

Clinical studies showed that Vemurafenib improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation (Chapman and al., 2011) suggesting that Vemurafenib effectively inhibited the MAPK pathway.

BRAF mutations have been detected in patients with non–small-cell lung cancer (NSCLC), with a lower frequency compared to melanoma. In the COSMIC database, BRAF mutations were observed in 1% of NSCLCs and a French study found 2% of BRAF mutations in 17 664 advanced NSCLC patients (Barlési, 2016).
Marchetti and colleagues have published data from a series of 1046 NSCLC patients with adenocarcinomas and squamous cell carcinomas. BRAF mutations were detected in respectively 4.9% and 0.9% of these histological subtypes. Authors have also reported a worse prognosis when BRAF mutation was located on the V600E position since those patients had shorter DFS (15.2 vs. 52.1 months; p<0.001) and OS (29.3 vs. 72.4 months; p<0.001) (Marchetti, 2011).

Clinical results with dabrafenib, a BRAF inhibitor, have been reported from a single-arm, phase II study in stage IV BRAF V600E mutation–positive NSCLC patients (Planchard, 2016). 84 patients were enrolled in this study, of which 78 previously pretreated patients showed an overall response rate of 33% (95% CI: 23.1-44.9) and 4 of 6 previously untreated patients had an objective response. This study gives clinical evidence of BRAF as a therapeutic target in NSCLC and then supports the interest of assessing vemurafenib in those patients who have limited therapeutic options.

Preliminary results of the French phase II basket trial, AcSé Vemurafenib, have been presented in the 2016 IASLC World Conference on Lung Cancer (Mazières 2016). 82 patients were included in the NSCLC BRAF mutation cohort. Among the 65 patients evalubale for efficacy, 56 harbored a BRAF V600 (E, D,K,M) mutation and 9 a BRAF non-V600 mutation. BRAF V600 mutation-positive patients showed an overall response rate at 16 weeks of 38.2% [25.9;51.3] (20 PR and 14 SD), a median PFS of 4.2 months [3.6;7.1] and a median OS of 8.7 months [5.6; NA], whilst BRAF non-V600 mutation-positive patients did not show any response nor stability. This study brings the confirmation of the interest of the BRAF V600 mutation as a therapeutic target for vemurafenib in NSCLC.

At this time, vemurafenib is FDA-approved for use only in BRAF V600E-mutated melanoma and promising activity in waiting for non-small cell lung cancer.

Cobimetinib, is an inhibitor of MEK, a protein involved in stimulating normal cell division. In melanoma with the BRAF V600 mutation, an abnormal form of the protein BRAF is produced, which switches on the protein MEK. This encourages the cancer to develop by allowing uncontrolled division of the cancer cells. It works by blocking MEK directly and by preventing its activation by the abnormal form of BRAF, thereby slowing down the growth and spread of the cancer. Cobimetinib is only given to patients whose melanoma is caused by the BRAF V600 mutation and must be used in combination with vemurafenib.

Cobimetinib has been studied in one main study involving 495 patients with melanoma that had spread or that could not be surgically removed, and whose melanoma had a BRAF V600 mutation. Patients had not been previously treated and were given either cobimetinib with vemurafenib or placebo (a dummy treatment) with vemurafenib; the main measure of effectiveness was how long patients lived without their disease getting worse (progression-free survival). In this study, adding cobimetinib to vemurafenib was more effective than adding placebo to vemurafenib: it took on average 12.3 months before the disease got worse in patients given cobimetinib, compared with 7.2 months in patients given placebo.

The Agency's Committee for Medicinal Products for Human Use (CHMP) decided on 20 November 2015 that cobimetinib's benefits are greater than its risks and recommended that it be approved for use in the EU. The Committee noted that cobimetinib in combination with vemurafenib had shown a clinically relevant benefit in patients whose melanoma had a BRAF V600 mutation, when compared with vemurafenib alone. Because cobimetinib and vemurafenib work by blocking different proteins important for cancer growth, combining them results in a better response and could delay cancer cells becoming resistant to vemurafenib. Although a supportive study showed that patients who were not previously treated with BRAF or MEK inhibitor medicines (such as vemurafenib) seemed to benefit the most from the therapy, the Committee considered that patients who previously received BRAF inhibitors may still benefit from treatment with cobimetinib and vemurafenib. In terms of safety, the side effects were considered acceptable and manageable with appropriate measures.

Clinical results with dabrafenib, a BRAF inhibitor, combined with trametinib, a MEK inhibitor, have been reported from a single-arm, phase II study in stage IV BRAF V600E mutation–positive NSCLC patients (Planchard, 2016). 57 patients previously treated with systemic chemotherapy were enrolled in this study. 36 patients have experienced a partial reponse and 4 a stable disease, for an overall response rate of 63.2% (95% CI: 49.3–75.6). Median PFS reached 8.6 months (95% CI: 5.2–19.1). The combination presented a manageable safety profile in patients with BRAF V600E–mutant NSCLC, in comparison to dabrafenib monotherapy. This study gives clinical evidence of the interest of dual MAPK pathway inhibition for NSCLC patients.

These data support the interest of assessing vemurafenib and cobimetinib as a maintainance therapy for NSCLC patients.

2.7. Immunotherapies in oncology

2.7.1. Rationale to develop immunotherapies in lung oncology

Recent data have suggested that blocking immune checkpoints could lead to major antitumor effects in patients with metastatic cancers. Although there are several immune checkpoints that could be targeted by immunotherapy, the leading target in this field is currently Programmed cell death 1 (PD-1). PD-1 is activated by PD-L1 and PD-L2, the two ligands. PD-L1 has been reported to be the predominant ligand in oncology. durvalumab is an anti-PD-L1 antibody. This drug has previously shown spectacular efficacy in patients with metastatic cancers. As illustration, durvalumab was associated with 46% and 35% of disease control in phase I patients (Lutskyet al, 2014) and lung cancer patients (Brahmer et al) respectively.
In the present study, we will evaluate the efficacy of durvalumab in patients with epidermoid and non-epidermoid lung cancer in a specific immune substudy.

2.7.2. Durvalumab (MEDI4736)

Durvalumab is a human monoclonal antibody that selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80. PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses by delivering inhibitory signals to T cells through the PD-1 and CD80 receptors. Blockade of PD-L1 with durvalumab relieved PD-L1-mediated suppression of human T-cell activation in vitro. In a xenograft model, durvalumab inhibited human tumor growth via a T-cell-dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and CTLA-4) resulted in tumor regression in a mouse model of colorectal cancer. In another combination therapy study, dual targeting of PD-1 and PD-L1 in a syngeneic model of sarcoma in mice demonstrated statistically significant mean tumor growth delay relative to the control group. Promising non-clinical data has been confirmed with results from clinical trials and as mentioned previously blocking the PD-1/PD-L1 pathway is an approach that has also been successfully employed with a number of approved anti-cancer therapies such as pembrolizumab (KEYTRUDA™), nivolumab (OPDIVO™) and atezolizumab (TECENTRIQ™).
As well as an extensive clinical programme assessing durvalumab across a wide array of solid tumours, durvalumab is also being studied as a monotherapy agent or in combination in a number of haematological indications including MDS relapsed/refractory lymphoma (Hodgkin or Non-Hodgkin) or relapsed/refractory chronic lymphocytic leukaemia, diffuse large B-cell lymphoma (DLBCL) and both newly diagnosed and relapsed/refractory multiple myeloma.

More than 5000 patients have been treated across a large number of studies with durvalumab given as either a single agent or in combinations with a number of other anti-cancer therapies. The studies are being conducted across various tumour indications and stages of disease, including solid tumours and haematologic malignancies. Encouraging clinical activity of durvalumab, combined with an acceptable and manageable safety profile, has been demonstrated across the monotherapy and combination therapy studies and are extensively described in the current Investigator's Brochure.
These data provide a sound rationale for further development in advanced solid tumors including breast and lung malignancies.

Altogether, this introduction has demonstrated that:

a. NSCLC includes a large number of diseases defined by a genomic aberration 'targetable' by a medication

b. we were able to carry out high throughput genomic analysis for clinical practice in a large study on solid tumors

c. the post-chemotherapy maintenance phase is a period during which there is no definitive standard of care. Pemetrexed in non-squamous patients and erlotinib in squamous is one option that is perfectly acceptable. Tumor progression appears rather quickly after the first line of chemotherapy in most patients.

In this study, we propose to compare maintenance targeted therapy guided by genomic analysis with maintenance therapy not guided by the analysis of the genome in patients with NSCLC without tumor progression at the end of induction chemotherapy.

3. OBJECTIVES OF THE TRIAL

3.1. Primary objective

To evaluate whether treatment with targeted agents guided by high throughput molecular analysis (CGH array, next generation sequencing) improves progression-free survival as compared to standard maintenance therapy in patients with metastatic NSCLC.

3.2. Secondary objectives

- To compare progression-free survival in patients treated with anti-PDL1 antibody (durvalumab) with those treated with maintenance therapy, in patients without actionable genomic alteration in the immune substudy 2 (primary objective of the substudy 2).
- To compare overall survival in each substudy.
- To compare overall response rates and changes in tumor size in each substudy.
- To evaluate safety, in each substudy
- To explore the efficacy (response rate, change in tumor size, progression-free survival, overall survival) and safety of each individual targeted agent in substudy 1.
- To perform a prospective pooled analysis of SAFIR02 Lung and SAFIR02 Breast studies
- To correlate molecular characteristics in patients with the efficacy endpoints (response rate, progression-free and overall survival) in each substudy.

3.3. Additional research objectives

- Circulating tumor DNA analysis to investigate: a/ correlation of ctDNA profiles with those obtained with NGS in the tumor sample; b/ identification of molecular alterations linked to resistance to targeted therapies.
- Validation of the functional protein activation and exploration of the sequence of events in the signalling pathways, using FISH and CISH, IHC staining, kinome arrays and RPPA analysis.
- Investigation of molecular changes that underlie disease progression and the formation of metastases a/ using whole exome sequencing program on normal cells, primary and metastatic tumor material; b / comparing the variation on molecular profiles from different metastatic sites Construction of a virtual cell to develop the optimal algorithm able to identify the driver alterations and then to deliver the optimal choice of therapy.

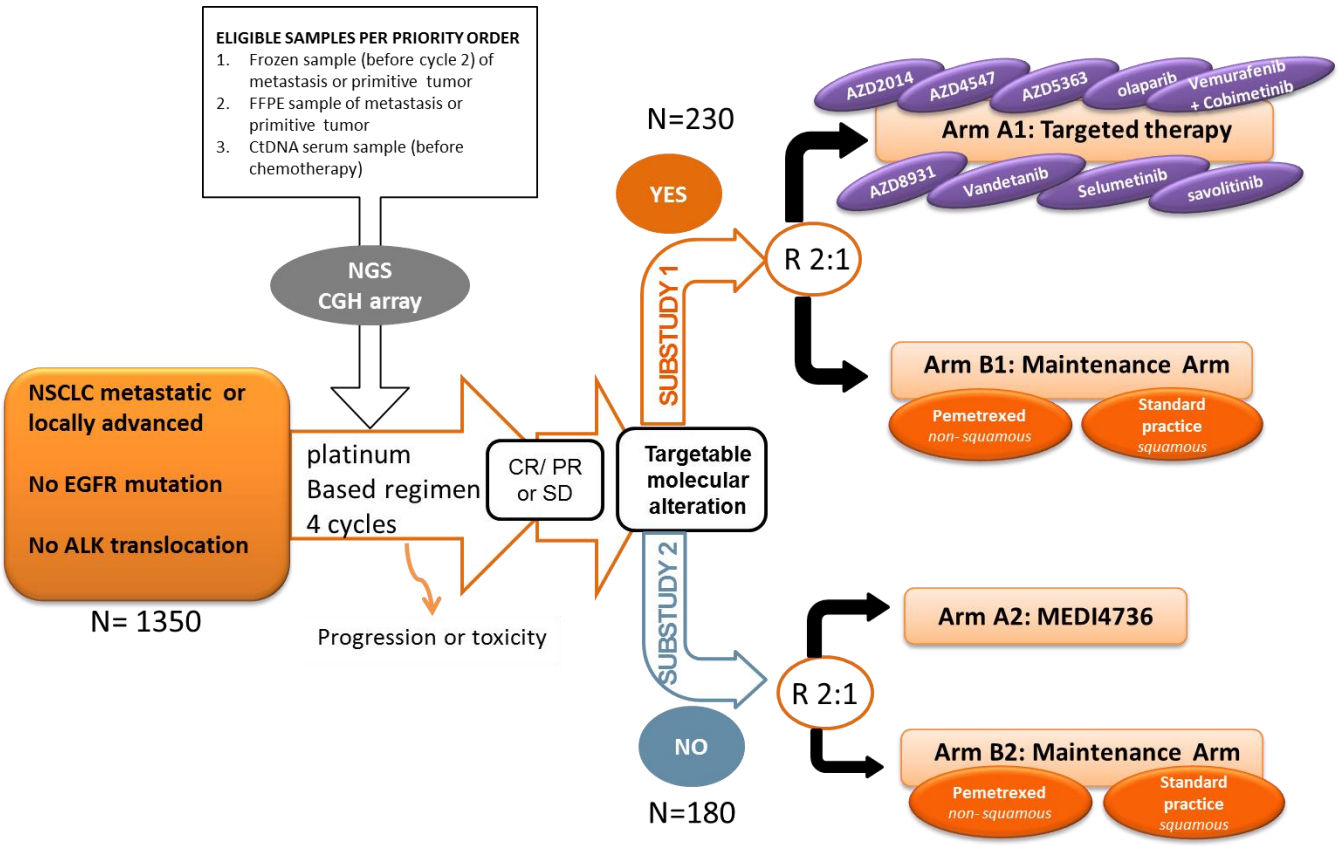
This research program is under the supervision of the steering committee which role is to consider how the projects should be modified in their objectives or in the technics they use, or even if they are still relevant in regards to the current state of scientific knowledge.

4. OUTLINE OF THE STUDY

4.1. Study design

SAFIR02 Lung is a biology driven, multicentric, randomized phase II trial designed to demonstrate that targeted treatment administered in accordance with genomic analysis of the tumor is more effective than standard maintenance treatment administered without genomic guidance (targeted substudy 1).
This study includes an exploratory substudy aimed at assessing the efficacy of immunotherapy compared to a maintenance therapy in patients without actionable genomic alterations or not eligible to a SAFIR02 targeted therapy (immune substudy 2).
The design of the trial is shown in the figure below. In this trial, high throughput analysis will be carried out using CGH arrays and next generation sequencing using a panel of around 70 genes.

Figure 5: Study scheme



The randomization program will allocate the following treatments with a 2:1 ratio in favor of Arm A:

Substudy 1 : targeted therapies versus standard maintenance therapy

- Arm A1 / targeted arm: targeted maintenance from a list of targeted drugs guided by the genomic analysis (refer to Table 1),

Or

- Arm B1 / standard arm: standard maintenance as per guidelines (refer to Table 1).

Substudy 2 : immunotherapy versus standard maintenance therapy

- Arm A2 / immunotherapy arm: durvalumab (refer to Table 1)

or

- Arm B2 / standard arm: standard maintenance as per guidelines (refer to Table 1)

Where disease progression occurs after randomisation in the standard arm (arm B), whatever the substudy, **a cross-over from arm B to arm A is not allowed.**

For substudy 1, the 2:1 randomisation will be stratified by histological subtype (squamous vs non-squamous), by tumor response (Stable disease vs Tumor response), by smoker/non-smoker and by molecular alteration as defined by the following categories:

- Category A: HER2 or RET aberration or FGFR1 amplification OR FGFR2 mutation OR FGFR3 mutation or any other aberration that is not in B, C, D
- Category B: no HER2**,** RET**,** FGFR1-2-3, LKB1 aberration but KRAS OR BRAF mutation
- Category C: no HER2, RET, FGFR1-2-3, LKB1**,** KRAS, BRAF aberration but PIK3CA mutation OR PIK3CA amplification OR PTEN loss OR PTEN mutation OR AKT1 mutation
- Category D: no HER2, RET, FGFR1-2-3, KRAS, BRAF, PIK3CA, PTEN, AKT1, aberration but LKB1 mutation

For substudy 2, the 2:1 randomization will be stratified by histological subtype (squamous vs non-squamous), by tumor response (Stable disease vs Tumor response) and by smoker/non-smoker.

Treatment allocation will be performed using minimization method as implemented in the randomization module of the e-CRF.

For each drug, Table 1 gives the description of the posology and the method of administration.
In all arms, treatments will be pursued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient refusal.

Table 1 : study drugs description and posology

Drug Name (IDN)	**Commercial Name**	**Pharmaceutical Form**	**Administration Route**	**Posology** (bd: twice daily, od: once daily, Q2W : every 2 weeks)
Investigational therapies				
Vistusertib	NA	tablet	per os	50 mg bd, continuous dosing
AZD4547	NA	tablet	per os	80 mg bd, 2 weeks on/1 week off
AZD5363	NA	tablet	per os	480 mg bd, 4 days on/3 days off
AZD8931	NA	tablet	per os	40 mg bd, continuous dosing
selumetinib	NA	capsule	per os	75 mg bd, continuous dosing
Vandetanib	CAPRELSA®	tablet	per os	300 mg od, continuous dosing
Olaparib	LYNPARZA®	tablets	per os	300 mg bd continuous dosing
Savolitinib	NA	tablets	per os	600 mg od continuous dosing (400 mg od for patient with body weight less than 50 kg)
Vemurafenib + Cobimetinib	Zelboraf®	tablets	per os	960 mg bd, continuous dosing
	Cotellic®	tablets	per os	60 mg od, 21 days on / 7 days off
Durvalumab	NA	liquid formulation	Intra-venous	10 mg/kg, Q2W
Standard maintenance treatments for non squamous NSCLC				
pemetrexed	ALIMTA®	powder for solution	Intra venous	500 mg/m^2, every 3 weeks
Standard maintenance treatments for squamous NSCLC				
Treatment is left to the investigator's decision as per local practice and shall be one of the 2 most common attitudes in France 1) Follow up with no active maintenance therapy 2) Gemcitabine				

Standard chemotherapies are prescribed as per usual practice and according to the product SmPC.

4.2. Endpoints

4.2.1. Primary endpoint : progression-free survival

Progression-free survival (PFS) is defined as the time from randomization to the first documented progression of disease or death, whatever the cause. The tumor assessments are made by the investigators based on RECIST 1.1 criteria ([Eisenhauer 2009]). Patients still alive at the time of analysis without documented progression (including lost of follow-up) will be censored at the last known alive date.

4.2.2. Secondary endpoints

4.2.2.1. Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Patients still alive at the time of analysis (including lost of follow-up) will be censored at the last known alive date.

4.2.2.2. Response and change in tumor size

Objective response (i.e. complete or partial response) will be defined using RECIST V1.1 criteria.
Changes in tumor size over time will also be analysed.

4.2.2.3. Safety

Evaluation of safety will be done according to NCI CTCAE v4.03 criteria.

4.2.3. Planned study duration

A 6 year accrual is planned for the screening of 1350 patients, recruitment of 230 patients in the randomized substudy 1 and 180 patients in randomized substudy 2. The expected treatment duration per patient is 4 months for targeted therapy and 6 months for durvalumab.
Total post-treatment follow-up period : 12 months in substudy 1, 24 months in substudy 2.
Whole estimated duration of the study : around 8 years

4.2.4. Trial early termination criteria

The trial can be suspended or stopped by the sponsor in agreement with the principal investigator and the Steering Committee, at the request of IDMC and/or the competent authority and/or the Committee for the Protection of Persons (CPP) for the following reasons:
- unexpected occurrence or severity of toxicity,
- insufficient patient recruitment,
- poor quality of data collection.

5. PATIENT SELECTION FOR THE MOLECULAR SCREENING PHASE

The following criteria will be verified for the screening phase eligibility.
The specific informed consent form for screening must be signed before any study procedure is undergone, including the biopsy.

5.1. Inclusion criteria

1. Patients with histologically proven NSCLC
2. Metastatic relapse or stage IV at diagnosis, or stage IIIb not amenable to surgery or radiotherapy.
3. No EGFR-activating mutation or ALK translocation for non-squamous NSCLC patients below 15 pack-year. For non squamous NSCLC patients above 15 pack-year and patients with squamous NSCLC, EGFR and ALK status are not mandatory at the time of inclusion but will need to be confirmed before randomization.
4. Patients with primary tumor or metastases that can be biopsied, excluding bone metastases. In the case a fresh biopsy collection is not achievable, patients able to provide a FFPE biopsy sample or a FFPE cytoblock will be considered as well. CtADN, ideally collected before chemotherapy initiation, will be a tertiary option in the following situation : existing tissue (fresh or FFPE) is not eligible for the study (i.e. <30% tumor cells, or

insufficient size) AND patients can not undergo a new biopsy (e.g. inaccessible location, or bone disease as the sole site, or patient real safety concerns).

5. Age > 18 years
6. WHO Performance Status 0/1
7. Chemo-naïve patients for their NSCLC management eligible to a first line platinum-based chemotherapy or currently receiving a first line platinum-based chemotherapy with a maximum of 2 cycles at the time of biopsy
8. No tumor progression observed with the current line of treatment
9. Presence of evaluable or measurable target lesion according to RECIST criteria v1.1
10. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses
11. Patient with social insurance coverage.

5.2. Exclusion criteria

1. Spinal cord compression and/or symptomatic or progressive brain metastases (unless asymptomatic or treated and stable without steroids during the last 30 days)
2. Patients with all target lesions in a previously irradiated region, except if clear progression has been observed prior to study in at least one of them
3. Patients who already had a genomic profile (both CGH and NGS analysis) in which no SAFIR02 targetable alterations have been identified
4. Inability to swallow
5. Major problem with intestinal absorption
6. Any of the following cardiac criteria:
   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG
   - Any factors increasing the risk of QTc prolongation or arrhythmic events such as heart failure, hypokalaemia, potential for torsades de pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years old or any concomitant medication known to prolong the QT interval.
   - Experience of any of the following procedures or conditions in the preceding 12 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, past or current uncontrolled angina pectoris (Canadian Cardiovascular Society grade II-IV despite medical therapy), congestive heart failure NYHA Grade ≥2, torsades de pointes, current uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy), cardiomyopathy
7. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which requires steroid treatment or any evidence of clinically interstitial lung disease
8. Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin.
9. Evidence of severe or uncontrolled systemic disease (active bleeding diatheses, or active Hepatitis B, C and HIV or any other serious active infection).
10. Previous history of myelodysplastic syndrome or acute myeloid leukaemia.
11. Medical diagnosis of acne rosacea, severe psoriasis and severe atopic eczema.
12. Prior exposure to anthracyclines or mitoxantrone with cumulative exposure in excess of 360 mg/m² for doxorubicin, 720 mg/m² for epirubicin, or 72 mg/m² for mitoxantrone (e.g for any other type of cancer occurred more than 5 years ago).
13. History of retinal degenerative disease, eye injury or corneal surgery in the previous 3 months, past history of central serous retinopathy or retinal vein occlusion, intraocular pressure >21 mmHg, or uncontrolled glaucoma.
14. Women who are pregnant
15. History of heamorrhagic or thrombotic stroke, TIA or other CNS bleeds
16. Renal disease including glomerulonephritis, nephritic syndrome, Fanconi syndrome, renal tubular acidosis

17. Patients using drugs that are known potent inhibitors or potent inducers or substrates of cytochrome P450 are not eligible if those treatments cannot be substituted during the randomized phase of the study.
18. Any condition which in the Investigator's opinion makes it undesirable for the subject to participate in the trial or which would jeopardize compliance with the protocol including recent history (past 12 months) of drug abuse or alcohol abuse.
19. Individuals deprived of liberty or placed under the authority of a tutor.

When all the criteria have been checked and patients are eligible for the screening phase, the registration procedure can be performed by the investigator (refer to section 8.2).

6. PATIENT SELECTION FOR THE RANDOMIZED THERAPEUTIC PHASE

6.1. Substudy 1: targeted therapies versus standard maintenance therapy

Patients can be considered as pre-eligible for randomisation in the substudy 1 when both following mandatory conditions are met :

- stable or responding disease is observed after 4 cycles of chemotherapy (investigator judgment)
- one targetable alteration is identified by the Molecular Tumor Board.

Then the patients will have to sign a second specific informed consent form for the randomization in the substudy 1 in order to initiate all the selection and baseline assessments. The mandatory post-chemotherapy wash-out period will provide time to achieve all the required tests and examinations.

Patients who cannot be randomized in the substudy 1 are patients who :
- failed to have a genomic profile for their tumor
- experienced disease progression during platinum-based chemotherapy or before randomization or didn't achieve 4 cycles of the platinum-based chemotherapy due to toxicities
- didn't present any targetable aberration in the genomic profile of their tumor
- present at least one exclusion criteria or didn't achieve all the inclusion criteria
- receive a decision from the Molecular Tumor Board contraindicating the randomization

Patients who can not be randomised in the targeted substudy 1 can be oriented to the immunotherapy substudy 2.

6.1.1. Inclusion criteria

1. Patients who received 4 cycles of an induction platinum-based chemotherapy and who are presenting a stable or a responding disease at the time of randomization
2. Patients who still meet the screening phase inclusion and exclusion criteria
3. EGFR and ALK status should be confirmed negative for all patients at this point
4. Patients whose tumor sample is presenting at least one genomic alteration from the list of predefined targetable genomic alterations and for whom the Molecular tumor board has provided a personalized guidance
5. Age > 25 years for patients planned to receive AZD4547
6. Patients will have had at least a 28-day washout period from the platinum-based regimen prior to randomization and should have recover (grade ≤1) from all residual toxicities, excluding alopecia.
7. Potentially reproductive patients must agree to use an effective contraceptive method (acceptable methods of contraception are described in section 9.1.1 and 10.1.1 of the protocol) while on treatment, beginning 2 weeks before the first dose of investigational product and for at least 4 months after the last dose of study drug. Male patients should refrain from fathering a child or donating sperm during the study and for at least 4 months following the last dose of study treatment.
8. Women of childbearing potential must have a negative serum pregnancy test done within 14 days and/or urine pregnancy test 72 hours prior to the administration of the study drug
9. Women who are breastfeeding should discontinue nursing prior to the first dose of study drug and until 3 months after the last dose.

10. Provision of signed and dated, written informed consent prior to randomization and to any study specific procedures, sampling and analysis
11. For patients supposed to be treated by savolitinib, adequate liver function defined as:

    -Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) with TBL≤ 1x ULN

    -OR TBL >ULN-≤1.5x ULN with ALT and AST ≤ 1x ULN

6.1.2. Exclusion criteria

1. No "targetable" genomic alteration identified during the screening phase (either due to the lack of alteration or due to ineligible samples for genomic analysis) or unfavorable decision from the Molecular tumor board to drive the patient to the randomization
2. Life expectancy < 3 months.
3. Disease progression occurring at any time during chemotherapy and before randomization or toxicity that led to the discontinuation of the platinum-based chemotherapy before 4 full cycles have been delivered,
4. Major surgery within 30 days (excluding placement of vascular access) or minor surgery within 14 days prior to randomisation
5. Less than 28 days from radiotherapy (wide field of radiation), less than 2 weeks from palliative radiation (limited fields). Fields should not have involved all target lesions
6. Patients previously treated for their metastatic disease with a targeted agent, the same or in the same class as the agent to be given to the patient in substudy 1.
7. Participation to another clinical study with an investigational product (IP) during the last 30 days
8. History of hypersensitivity to active or inactive excipients of one of the study drugs
9. Toxicities of grade ≥2 from any previous anti-cancer therapy, with the exception of alopecia
10. Altered haematopoietic or organ function, as indicated by the following criteria:
    - Polynuclear neutrophils < 1.5 x 10^9/L
    - Platelets < 100 x 10^9/L
    - Haemoglobin < 90 g/L or Haemoglobin < 100 g/L and no blood transfusion within 28 days for olaparib)
    - ALAT/ASAT > 2.5x ULN in the absence of or > 5x ULN in the presence of liver metastases
    - bilirubin > 1.5xULN
    - creatinine clearance ≤50 mL/min (measured or calculated by Cockroft and Gault formula)
    - Proteinuria > 3+ on dipstick analysis or > 3.5g/24 hours or a urine protein/creatinine ratio > 3.5 (only for patients dried to receive AZD5363)
    - Sodium, magnesium, calcium and phosphate > ULN or < LLN
    - Potassium < LLN or > ULN or (Potassium < 4 mmol/L or > ULN for vandetanib)
11. Any of the following additional cardiac criteria:
    - Mean resting corrected QT interval (QTc)>480msec (or QTcF >450 msec) obtained from 3 consecutive ECGs
    - LVEF <55% (MUGA scan or Echocardiogram),
12. Altered ophthalmic conditions confirmed by an ophthalmology specialist for patients likely to be treated with :
    - AZD4547 : current evidence or previous history of retinal pigmented epithelium detachment (RPED), previous laser treatment or intra-ocular injection for treatment of macular degeneration, current evidence or previous history of dry or wet age-related macular degeneration, current evidence or previous history of retinal vein occlusion (RVO), current evidence or previous history of retinal degenerative diseases (eg, hereditary), current evidence or previous history of any other clinically relevant chorioretinal defect
    - Selumetinib : intraoccular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure), current or past history of retinal pigment epithelial detachment or central serous retinopathy or retinal vein occlusion
13. Clinically significant abnormalities of glucose metabolism, for patients supposed to be treated by vistusertib or AZD5363, as defined by any of the following:
    - For vistusertib :
        - Diagnosis of diabetes mellitus type I or II (irrespective of management)
        - Glycosylated haemoglobin (HbA1C) ≥ 8.0% (64 mmol/mol)
        - Fasting Plasma Glucose ≥ 7.0 mmol/L (126 mg/dL) (fasting is defined as no calorie intake for at least 8 hours)

- For AZD5363 :
  - Diabetes mellitus type I
  - Fasting plasma glucose (fasting is defined as no calorific intake for at least 8 hours): ≥ 7.0mmol/L (126 mg/dL) for those patients without a pre-existing diagnosis of Type 2 diabetes mellitus OR ≥ 9.3 mmol/L (167mg/dL) for those patients with a pre-existing diagnosis of Type 2 diabetes mellitus
  - Requirement for insulin for routine diabetic management and control
  - Requirement for more than two oral hypoglycaemic medications for routine diabetic management and control

14. Patients using drugs that are known potent inhibitors or potent inducers or substrates of cytochrome P450 are not eligible if those treatments cannot be substituted from 14 days prior to the first dose (except those for which the minimum wash-out period is longer, e.g Fluoxetine and Phenobarbital: 5 weeks, Rifabutin : 3 weeks and amiodarone: 27 weeks) and during the study.
15. Patients using non-substitutable drugs, that are known to prolong QT interval or induce Torsades de Pointes, from 14 days prior to the first dose (except those for which the minimum wash-out period is longer) and during the study, are not eligible when they are supposed to be treated with vandetanib or AZD5363.
16. Known clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis for patients likely to be treated with savolitinib.

    Patients with a past or resolved HBV infection are eligible if:

    - negative for HBsAg and positive for hepatitis B core antibody [anti-HBc] or
    - positive for HBsAg, but for > 6 months have had normal transaminases and HBV DNA levels between 0 – 2000 IU/ml (inactive carrier state) and willing to start and maintain antiviral treatment for at least the duration of the study.
    - HBV DNA levels >2000 IU/ml but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study

    Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV RNA.

17. For patients likely to be treated with vistusertib, patients exposed to strong or moderate inhibitors or inducers of Pgp (MDR1) and BCRP are not eligible if those treatments cannot be substituted from 14 days prior to the first dose and during the study. Patients exposed to specific substrates of the drug transporters OATP1B1, OATP1B3, MATE1 and MATE2K are not eligible if those treatments cannot be substituted from a minimum of 5 x reported elimination half-life prior to the first dose and during the study.
18. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug.

When all the criteria have been checked and are met, and after the mandatory 28-day period has elapsed, the randomization procedure can be performed by the investigator (refer to section 9.2).

6.2. Substudy 2: Immunotherapy versus standard maintenance therapy

Patients can be considered as pre-eligible for the randomization phase in the immune substudy 2 when both following mandatory conditions are met:

- stable or responding disease (investigator judgment) is observed after 4 cycles of chemotherapy (investigator judgment) **AND**
- not eligible to randomization in the targeted substudy 1 because patient had :
  - no targetable alteration identified by the Molecular Tumor Board, or
  - failed to have a genomic profile for the tumor (low tumor cells percentage, technical issue during genomic analysis, etc.), or
  - a non inclusion criteria that precluded entry into the targeted substudy 1

Then the patients will have to sign a second specific informed consent form for the randomization phase in the immune substudy 2 in order to initiate all the selection and baseline assessments. The mandatory post-chemotherapy wash-out period will provide time to achieve all the required tests and examinations.

Patients who cannot be randomized in the immune substudy 2 are patients who:
- experienced disease progression during platinum-based chemotherapy or before randomization or didn't achieve 4 cycles of the platinum-based chemotherapy due to toxicities
- present at least one exclusion criteria or didn't achieve all the inclusion criteria
- receive a decision from the Molecular Tumor Board contraindicating the randomization

Non randomized-patients will not be monitored but some informations on their cancer treatments, the disease progress and vital status will be collected during 2 years from the date of inclusion in the screening phase (refer to section 10.6.2).

6.2.1. Inclusion Criteria

1. Patients who received 4 cycles of an induction platinum-based chemotherapy and who are presenting a stable or a responding disease at the time of randomization
2. Patients who still meet the screening phase inclusion criteria and exclusion criteria excluding exclusion criteria 16.
3. Patients not eligible to substudy 1
4. EGFR and ALK status should be confirmed negative for all patients at this point
5. Patients will have had at least a 28-day washout period from the platinum-based regimen prior to randomization and should have recover (grade ≤1) from all residual toxicities, excluding alopecia.
6. Potentially reproductive patients must agree to use an effective contraceptive method (acceptable methods of contraception are described in section 9.1.1 and 10.1.1 of the protocol) while on treatment, beginning 2 weeks before the first dose of investigational product and for at least 4 months after the last dose of study drug. Male patients should refrain from fathering a child or donating sperm during the study and for at least 4 months following the last dose of study treatment.
7. Women of childbearing potential must have a negative serum pregnancy test done within 14 days of enrollment and/or urine pregnancy test 72 hours prior to the administration of the study drug.
8. Women who are breastfeeding should discontinue nursing prior to the first dose of study drug and until 4 months after the last dose.
9. Provision of signed and dated, written informed consent prior to randomization and to any study specific procedures, sampling and analysis.

6.2.2. Exclusion Criteria

1. Life expectancy < 3 months.
2. Disease progression occurring at any time during chemotherapy and before randomization or toxicity that led to the discontinuation of the platinum-based chemotherapy before 4 full cycles have been delivered
3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab
4. Participation to another clinical study with an investigational product (IP) during the last 30 days
5. Toxicities of grade ≥2 from any previous anti-cancer therapy, with the exception of alopecia.
6. Altered haematopoietic or organ function, as indicated by the following criteria:
7. Polynuclear neutrophils < 1.5 x 109/L
8. Platelets < 100 x 109/L
9. Haemoglobin < 90 g/L
10. ALAT/ASAT > 2.5x ULN in the absence of or > 5x ULN in the presence of liver metastases
11. bilirubin > 1.5xULN. This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician

12. serum creatinine clearance ≤40 mL/min (measured or calculated by Cockroft and Gault formula) or by 24-hour urine collection for determination of creatinine clearance
13. Mean resting QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 consecutive ECGs using Bazett's Correction
14. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent of other corticosteroid
15. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded
1. Active or prior documented inflammatory disease (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone
16. History of primary immunodeficiency
17. History of allogeneic organ transplant
18. History of hypersensitivity to durvalumab or any excipient
19. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, serious chronic gastrointestinal conditions associated with diarrhea, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B (patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg are eligible), hepatitis C (patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA) or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
20. Known history of previous clinical diagnosis of tuberculosis
21. History of leptomeningeal carcinomatosis
22. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab
23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
24. Subjects with uncontrolled seizures
25. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP (Note: Local surgery of isolated lesions for palliative intent is acceptable)

7. TREATMENTS

7.1. Investigational drugs description

Vistusertib is an orally administered selective inhibitor of the kinase activity of mammalian target Of Rapamycin (mTOR). mTOR is a serine/threonine kinase belonging to the PI3K (PIKK) superfamily of kinases. Vistusertib inhibits signaling of mTOR complexes, mTORC1 and mTORC2.

AZD4547 is an oral, potent and selective inhibitor of FGFR-1, 2 and 3 receptor tyrosine kinases (enzyme and cellular phosphorylation endpoints), and has a significantly lower potency for inhibition of IGF1R and KDR.

AZD5363 is an orally administered potent, selective inhibitor of the kinase activity of the serine/threonine kinase AKT/protein kinase B (PKB) that is being developed as a potential treatment for solid malignancies.

AZD8931 is an oral, equipotent inhibitor against EGFR, erbB2 and erbB3 for the treatment of solid tumors.

Selumetinib (AZD6244) is an orally administered potent, selective, uncompetitive inhibitor of MEK. Its activity may be primarily seen in tumors harbouring mutated RAS or RAF genes.

Vandetanib (Caprelsa®, ZD6474) is an oral potent inhibitor of the tyrosine kinase activity of VEGFR (also known as kinase insert domain containing receptor-2) involved in angiogenesis, and also possesses activity against EGFR and RET tyrosine kinases involved in tumor cell growth.

Olaparib (Lynparza®) is an orally administered potent inhibitor of poly (ADP-ribose) polymerase enzyme (PARP). As a single agent, olaparib is active in tumours with defective components of homologous recombination that includes those with BRCA1-/- and BRCA2-/- mutations.

Savolitinib (AZD6094) is an orally administered potent inhibitor of MET kinase when tumor are MET mutated or where amplification are identified.

Vemurafenib (Zelboraf®) is an orally administered potent inhibitor of BRAF that specifically targets the V600E isoform. The result of the BRAF V600E mutation is an abnormal form of the protein BRAF, which switches on the protein MEK.

Cobimetinib (Cotellic®) is an orally administered inhibitor of MEK. Cobimetinib will inhibit this protein MEK switch on by the abnormal BRAF protein.

Durvalumab (MEDI4736) is an IV administered human IgG1κ monoclonal antibody directed against PDL1, and with reduced binding to C1q and the Fcγ receptors.

7.2. Standard therapies

For non-squamous NSCLC : **Pemetrexed** (Alimta®) is an intravenous inhibitor of folate-dependent enzymes involved in purine and pyrimidine synthesis, preventing tumor growth.

For squamous NSCLC **:** The most common attitudes in France are
- the therapeutic pause : follow-up with no active maintenance therapy
- **Gemcitabine** (Gemzar®) : gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP.

7.3. Drug supply, composition and packaging, labeling, storage conditions

The investigational drugs: vistusertib, AZD4547, AZD5363, AZD8931, selumetinib, vandetanib, olaparib, savolitinib and durvalumab will be supplied by Unicancer (provided by AstraZeneca Pharmaceuticals). Vemurafenib and cobimetinib will be supplied by Unicancer (provided by Roche).

Table 2 : drugs presentations and storage conditions

Investigational Drug	Presentation	Storage conditions
Vistusertib	10 and 25 mg tablets: plain, round, biconvex, yellow film-coated tablets	At room temperature (15-25°C)
AZD4547	tablets 20 mg and 80 mg: plain, round, biconvex, white, film-coated tablets	
AZD5363	Tablets 80 and 200 mg : beige film coated tablets	
AZD8931	20 mg and 40 mg tablets: plain, round, biconvex white or beige film-coated tablets.	

Selumetinib (AZD6244)	25 mg capsules: plain, blue HPMC capsules.	
Vandetanib (Caprelsa®, ZD6474)	100 mg and 300 mg tablets: white film-coated tablets.	
Olaparib (Lynparza®, AZD2281)	100 mg and 150 mg: green film-coated tablets	
Savolitinib (AZD6094)	200 mg film-coated oval yellow tablets	
Vemurafenib (Zelboraf®)	240 mg pinkish white to orange white, oval, biconvex film-coated tablets	
Cobimetinib (Cotellic®)	20 mg film-coated white, round, tablets	
MEDI4736	Liquid formulation : each vial contains 500mg of active investigational product at a concentration of 50mg/mL (500mg/vial).	Unopened vials of liquid durvalumab must be stored at 2°C to 8°C . Total in-use storage time from needle puncture of durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C. If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. durvalumab does not contain preservatives and any unused portion must be discarded.

All the investigational drugs, except durvalumab, will be supplied in tamper-evident and child-resistant HPDE bottles and labeled in accordance with the clinical trials specific requirements and regulations.
durvalumab will be supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal, and labeled in accordance with the clinical trials specific requirements and regulations.

Drugs used for the maintenance chemotherapy will be provided by the center's pharmacies.

7.4. Ordering, dispensing, accountability and destruction

Treatment initiation
As soon as the Molecular Tumor board has given an orientation to a patient, and if the patient is still eligible for the randomization, a batch containing three cycles of the oriented tinvestigational agent or four cycles if durvalumab will be supplied to the site's pharmacy.

If the randomization procedure has allocated the investigational drug (2/3 chances), the next supply of three cycles (four cycles for durvalumab) of treatment will be addressed to the site 6 weeks later on.
In the case the randomization procedure has allocated the standard arm (1/3 chances), the batch will be kept at the pharmacy for another patient.

The site pharmacist will confirm the reception as described in Table 3:

The investigator will then forward to his/her pharmacist the SAFIR02 prescription form. Centers are permitted to use their internal prescription forms or dedicated software providing they collected equivalent information.

Treatment resupply

Resupply will be provided approximately every 6 weeks without any action from the pharmacist. Resupply management system is described in Table 3.

All drug strengths will be provided. In case of dose reduction, the pharmacist will have to notify the information as outlined in Table 3.

End of treatment
End of treatment should be rapidly notified to the sponsor SAFIR02 team (by phone or e-mail). Such information can arise either from the pharmacy or from the investigator.
Informations to be recorded are detailed in Table 3.

Delivery conditions
A maximum of 86 hours (4 working days) are warranted between the order initiation and the treatment delivery. Delivery will be made exclusively in the center's pharmacy.

Dispensing to the patient
Oral study drugs will be dispensed to the patient every cycle. Patients should be requested to bring back all used or unused bottles of treatment at every 3-week consultation.
Intra-venous study drugs (durvalumab) will be diluted and strictly administered at hospital.
Only patients enrolled in the study may receive the investigational products, in accordance with all applicable regulatory requirements. Only the investigator, the site pharmacy or authorized on-site personnel may supply or administer the investigational products.

Drug accountability
Investigational drugs supplies accountability should be accurately maintained by each site as outlined in Table 3.

Accountability of the remaining tablets or capsules will be documented and recorded under the responsibility of the pharmacist.
Destruction forms will be provided to the pharmacies. Centers are permitted to use their internal procedures providing they collect equivalent informations.

There is no accountability requested by the protocol for standard therapy (arm B).

Table 3 : drugs traceability procedures

Drugs	vistusertib, AZD4547, AZD5363, AZD8931, selumetinib, vandetanib, olaparib, savolitinib and durvalumab	vemurafenib and cobimetinib
Pharmaceutical services provider	Fisher Clinical Services UK, Langhurst Wood Road, Horsham, RH12 4QD, United Kingdom.	Pharmaceutical service provider in France. To be defined
Drug management system	IWRS	Sponsor management
Reception	Has to be confirmed using an IWRS (Interactive Web Response Services)	Has to be confirmed on specific forms provided by the Sponsor
Resupply	No action from the pharmacist. Automated though the IWRS	No action from the pharmacist. Directly managed by the Sponsor
Dose reduction	The prescribed dose should be rapidly registered in the IWRS	Any dose reduction should be rapidly notified to the Sponsor
End of treatment	Has to be rapidly notified to the sponsor, recorded in the e-CRF and IWRS	Has to be rapidly notified to the sponsor and recorded in the e-CRF
Drug accountability	Receipt dates, batch numbers, expiry dates, quantities, patients dispensation, destruction dates, relevant remarks or issues, should be completed in the IWRS for AstraZeneca treatments. Stock balance for each drug will be calculated by the system according to the registered information. Per patient drug supply will appear in the IWRS with patient identification number, batch numbers, expiry dates, dates of delivery and return, quantities delivered and returned.	Receipt dates, batch numbers, expiry dates, quantities, patient dispensation, destruction dates, relevant remarks or issues, should be completed in the specific forms provided by the sponsor. Stock balance will be calculated by the site personnel on dedicated forms or on internal forms or systems.

7.5. Role and liabilities of institutions involved in the medication circuit

7.5.1. Clinical supply services provider

Packaging, labeling and distribution for investigational drugs will be subcontracted to 2 different pharmaceutical services providers, presented in Table 3.

Labeling will be made in accordance with the guidelines of the appendix 13 of the EEC directive: Good Manufacturing Practices for the manufacture of investigational medicinal products (revised and adopted on 30 January 2010 by the European Commission). The distribution of the investigational drug to the participating centers' pharmacies will be performed in conformity with the Good Distribution Practices, under sponsor's supervision and responsability.

7.5.2. Sponsor

Unicancer will be responsible for obtaining all required documents from the center, in accordance with applicable regulatory requirements, to authorize the distribution of each investigational drug on site.

It is the responsibility of Unicancer to give a distribution agreement to the pharmaceutical services provider for any individual re-supply demand from the investigational site. Unicancer will perform possible audits of the pharmacy for control of investigational drug storage conditions, traceability and adequate patient delivery conditions according to the protocole requirements.

7.5.3. Investigator and center's pharmacy

Stock management is under the responsibility of the pharmacist. The pharmacist will acknowledge reception of all shipments as explained in Table 3.

Investigational medicinal products will have to be stored in locked room with limited access and in accordance with the recommendations of the manufacturer (refer to Table 2: drugs presentations and storage conditions).

The pharmacist will keep accurate records of the drugs delivered, used, unused and/or returned by the patient or destroyed, and will capture the data in the systems presented in Table 3.

7.6. Treatment course

7.6.1. Dosage and administration

7.6.1.1. General conditions of administration

For the oral investigational therapies, cycles are defined :

-in 21-day periods for vistusertib, AZD4547, AZD5363, AZD8931, selumetinib, vandetanib, olaparib and savolitinib

-in 28-day periods for vemurafenib+cobimetinib.

Study treatment will be pursued until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient refusal.

Oral study drugs will be dispensed to the patients on the first day of treatment, after it has been confirmed that the patients meet all eligibility criteria, all screening assessments have been completed, the results reviewed, and randomization performed.

Study staff will carefully instruct patients how to take oral study drugs. All oral drugs should be taken at approximately the same time every day. Interactions with food are detailed in Table 4 and conditions of administration should be explained to the patient.

Tablets and capsules should not be crushed or opened respectively, and should be swallowed with a glass of water.

Any missed dose may be taken up to a maximum of 2 hours after the scheduled dose time, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. Missed doses will be reported in the CRF.

If a patient vomits after taking one of the investigational oral drugs, the patient should be instructed not to retake the dose, unless capsules or tablets are intact and can all be counted. Patients should take the next scheduled dose of the drug. If vomiting persists, then the patients must contact the investigator.

Investigational oral drugs dose modification guidelines are outlined in section 7.6.2. and should be used for the management of treatment-related toxicities. Patients should be carefully instructed when any dose modifications occurs.

Any of the investigational drugs **should not** be re-escalated to an earlier dose level on improvement of an AE.

NOTE : oral **investigational** study drugs should NOT be taken with grapefruit, star fruit, pomegranate, Seville oranges, and other similar fruits. All these fruits or derivated products are not permitted for the duration of the study.

For durvalumab, cycles are defined in 14-day periods. Treatment with durvalumab commences on Day 1 following confirmation of eligibility into the substudy 2 (and after a 28-day wash out from cycle 4 of chemotherapy) and continues on a Q2W schedule until progression. Study treatment should be discontinued prior to 12 months if there is confirmed disease progression, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.
Subjects who have a dose interruption due to toxicity at any point in the first 12 months of treatment may resume treatment and complete the 12-month treatment period.

Standard therapies should be administered and dose reduced according to Summary of Product Characteristics recommendations and local standard practice.

7.6.1.2. Specific conditions of administration

Table 4 : specific posology and methods of administration

Drug Name (IDN)	Commercial Name	Pharmaceutical Form and dosage	Administration Route	Posology (bd: twice daily, od: once daily)	Method of administration
INVESTIGATIONAL DRUGS					
Vistusertib	NA	10mg and 25mg tablets	per os	50 mg bd, continuous dosing	Tablets should be taken at least one hour before or two hours after the ingestion of food or drinks (other than water). Sugary and fatty foods should be avoided in the meals prior to taking a dose.
AZD4547	NA	20mg and 80mg tablets	per os	80 mg bd, 2 weeks on/1 week off	Tablets can be taken without regards to food, but always approximately at the same time
AZD5363	NA	80mg and 200mg tablets	per os	480 mg bd, 4 days on/3 days off	Tablets should be taken at least one hour before or two hours after the ingestion of food or drinks (other than water).
AZD8931	NA	20mg and 40mg tablets	per os	40 mg bd, continuous dosing	Tablets can be taken without regards to food, but always approximately at the same time
Selumetinib	NA	25mg capsules	per os	75 mg bd, continuous dosing	Capsules should be taken at least one hour before or two hours after the ingestion of food or drinks (other than water)
Vandetanib	CAPRELSA®	100mg and 300mg tablets	per os	300 mg od, continuous dosing	Tablets can be taken without regards to food, but always approximately at the same time
Olaparib	LYNPARZA®	100mg and 150mg tablets	per os	300 mg bd, continuous dosing	Tablets can be taken without regards to food, but always approximately at the same time
Savolitinib	NA	200 mg tablets	per os	600 mg od, continuous dosing (400 mg od for patient with body weight less than 50 kg)	Tablets should betaken in the fed state, approximately at the same time
Vemurafenib	Zelboraf®	240 mg tablets	per os	960 mg bd, continuous dosing, in combination with cobimetinib	Vemurafenib may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided.
Cobimetinib	Cotellic®	20 mg tablets	per os	60 mg od, 21 days on / 7 days off, in combination with vemurafenib	Tablets can be taken without regards to food, but always approximately at the same time Cobimetinib may be taken at the same time as vemurafenib.
Durvalumab	NA	500mg liquid for	Intra-venous	10 mg/kg, Q2W	Durvalumab will be administered at room

		infusion at a concentration of 50mg/mL (500mg/vial). The solution will be diluted with 0.9% (W/v) saline for IV infusion			temperature (approximately 25°C) as an IV infusion over approximately 60 minutes (±5 minutes). Durvalumab calculation dose, preparation and administration are outlined in Appendix 13.
STANDARD MAINTENANCE TREATMENTS					
Posology and method of administration will follow SmPc recommendations and standard practice					

7.6.2. Dose reduction and guidelines for management of toxicities

For standard maintenance treatment, follow the local practice or SmPC.

7.6.2.1. Vistusertib

Table 5 : Vistusertib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Fatigue	
Grade 1-2	**Continue at the same dose level**
Grade ≥3	**Withhold current dose for up to 14 days until grade ≤ 2 and resume treatment at lower dose.**
Stomatitis/ oral mucositis/ mouth ulcers	
Grade 1	**For mild toxicity, treatment can be continued at the same dose.**
Grade 2 or 3	**1st occurrence : withhold current dose for up to 14 days until stomatitis improves to grade ≤ 1, and then resume to the same dose** **2nd occurrence: resume treatment at a lower dose.** **If initial grade 3 reverts to grade ≤ 2 within 14 days, and the patient is showing clinical benefit, treatment may be restarted at the same dose or dose reduced upon investigator judgment.** **If the toxicity does not resolve to grade ≤ 2 after 14 days, then treatment should be permanently discontinued and patient observed until resolution**
Grade 4	**Permanently discontinue treatment**
Thrombocytopenia	
Grade 1	**Continue at the same dose level**
Grade 2 or 3	1st occurrence: withhold current dose for up to 14 days until recovery to grade ≤1. Then, resume treatment at reduced dose. 2nd occurrence: permanently discontinue treatment
Grade 4	**Permanently discontinue treatment if toxicity persists more than 4 days**
Specific conditions	**Patients who begin Warfarin or Coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving vistusertib and should stop medication when thrombocytopenia Grade ≥ 3.**
Anemia	
Grade 1	**Continue at the same dose level**
Grade 2 or 3	1st occurrence: withhold current dose for up to 14 days until recovery to grade ≤1. Then, resume treatment at reduced dose. **2nd occurrence: permanently discontinue treatment**
Grade 4	**Permanently discontinue treatment.**
Lymphopenia	
Grade 2 800/mm^3 (0.8x10e9/L) >lymphocyte count ≥ 500/mm^3 (0.5x10e9/L)	1st occurrence: interrupt dose until recovery to grade 0 or baseline level, then restart at reduced dose. **2nd occurrence: permanently discontinue treatment**

or Grade 3 500/mm^3 (0.5x10e9/L) >lymphocyte count ≥ 200/mm^3 (0.2x10e9/L)	
Grade 4 200/mm^3 (0.2x10e9/L) > lymphocyte count	**Permanently discontinue treatment**
Specific conditions	In case of opportunistic infection or tuberculosis or visceral fungal infection; discontinue treatment. In case of recurrent non-opportunistic, non-life threatening infections (at least 3 in the last 3 months): reduce dose level. In case of life-threatening infection (septicemia, pneumonia requiring 0_2 support, meningitis…): discontinue treatment.
Pneumonitis/ Interstitial lung disease (not due to disease progression, other pulmonary disease, infection or radiation effect)	
Grade 1	Continue at the same dose level
Grade 2 or 3	1st occurrence: Interrupt dose for up to 28 days until recovery to Grade ≤ 1, then, restart at reduced dose. Permanently discontinue treatment if toxicity fails to recover to grade ≤1 within 28 days. 2nd occurrence: permanently discontinue treatment.
Grade 4	Permanently discontinue treatment.
Hyperglycemia	
Grade 1 : FPG < 8.9 mmol/L (160mg/dL)	Continue at the same dose level
Grade 2 : 8.9≤FPG<13.9 mmol/L (160mg/dL-250mg/dL)	If patient is asymptomatic, continue at the same dose level. If patient presents with signs or symptoms*, withhold current dose for up to 28 days and consider appropriate management (refer to section 12.1.3.2 for hyperglycemia guidelines)
Grade 3 : 13.9≤FPG<27.8 mmol/L (250mg/dL-500mg/dL)	If patient is asymptomatic, withhold current dose for up to 28 days and consider appropriate management. If patient presents with signs or symptoms*, withhold current dose for up to 28 days and consider appropriate management. Then monitor FPG as per local guidelines and : • If FPG <8.9mmol/L (160mg/dL) within 48h, resume study treatment at the same dose, and continue treatment for hyperglycemia • If FPG < 8.9mmol/L (160mg/dL) after 48h and before 28 days, resume study treatment at a lower dose, and continue treatment for hyperglycemia • If FPG persists ≥ 8.9mmol/L (160mg/dL), permanently discontinue study treatment within 48h, resume study treatment at the same dose, and continue treatment for hyperglycemia
Grade 4 : FPG>27.8 mmol/L (500mg/dL)	Permanently discontinue treatment
	*polyphagia, polydipsia, polyuria, dizziness, systolic blood pressure <100mmHg, symptoms of ketoacidosis such as breath that smells fruity, nausea, vomiting, mouth extremely dry, short of breath
Cholesterolemia	
Grade 2 : 300<CT<400 mg/dL (7.75-10.34 mmol/L)	Continue at the same dose level
Grade 3 : 400≤CT<500 mg/dL (10.34-12.92	Reduce treatment to lower dose and consider concomitant management for cholesterolemia

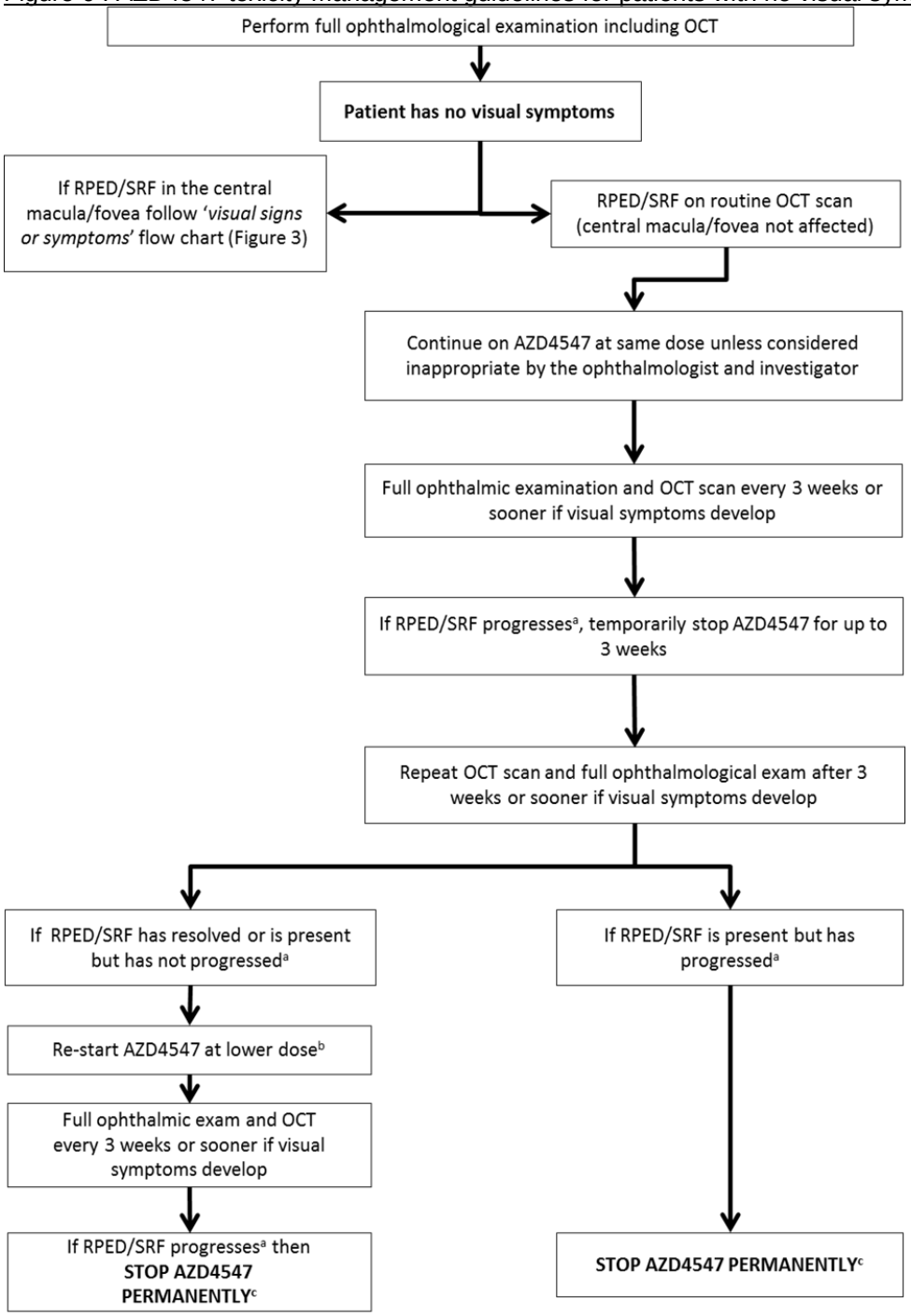
mmol/L)	
Grade 4 : CT ≥ 500 mg/dl (12.92 mmol/L) despite optimal management of cholesterolemia	Permanently discontinue treatment
T-Wave inversion	
	Continue at the same dose level, with full panel of cardiac investigations strictly monitored as per protocol (refer to section 12.1.3.4) Permanently discontinue treatment when : • Any clinically significant, new or worsening symptoms and/or signs that are confirmed to be of a cardiac origin • Troponin T increase 3 fold from baseline (CTC grade 3) and significant changes in CK/CK-mb ratio (relative index >5%). If only Troponin T is raised, re-confirmed after 12 h; new ECHO and Data Safety Monitoring Board will be consulted • Clinically significant increase in heart rate of +25 bpm (up to 100-125 bpm for more than 24 h or increase in heart rate >125 bpm for more than 12 h) • Recurrent or persistent (>24 h) or symptomatic increases in blood pressure (increases by >20 mmHg diastolic or >165/100 mmHg) despite standard antihypertensive treatment • QTc prolongation (>500 msec)
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable Grade 2 Grade 3	1st occurrence : withhold current dose for up to 14 days until toxicity improves to grade ≤ 1, and then resume to the same dose 2nd occurrence: resume treatment at a lower dose. If initial grade 3 reverts to grade ≤ 2 within 14 days, and the patient is showing clinical benefit, treatment may be restarted at the same dose or dose reduced upon investigator judgment. If the toxicity does not resolve to grade ≤ 2 after 14 days, under optimal supportive therapy, then treatment should be permanently discontinued and patient observed until resolution
Grade 4	Permanently discontinue treatment

7.6.2.2. AZD4547

Table 6 : AZD4547 management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Ophthalmic toxicity	
If no visual symptoms	**Refer to Figure 6 : AZD4547 toxicity management guidelines for patients with no visual symptoms of ocular toxicity for management guidelines**
If visual signs or symptoms	Refer to Figure 7 : AZD4547 management guidelines for patients with visual symptoms of ocular toxicity for management guidelines
Hyperphosphatemia	
If corrected Ca:PO_4 product > 4.5 $mmol^2/l^2$ Or If doubling in PO_4 from baseline	Continue AZD4547 at the same dose level and start phosphate chelation therapy as clinically appropriate. If toxicity resolves continue chelation therapy and current AZD4547 dose . If toxicity does not resolve before 14 days, continue chelation therapy, reinstate AZD4547 at tone dose level lower, except if already at Dose-2 then AZD4547 will be permanently discontinued.
Stomatitis/ oral mucositis/ mouth ulcers	
Grade 1	Continue at the same dose level.
Grade 2 or 3	1st occurrence : withhold current dose for up to 14 days until stomatitis improves to grade ≤ 1, and then resume to the same dose 2nd occurrence: resume treatment at a lower dose. If initial grade 3 reverts to grade ≤ 2 within 14 days, and the patient is showing clinical benefit, treatment may be restarted at the same dose or dose reduced upon investigator judgment. If the toxicity does not resolve to grade ≤ 2 after 14 days, then treatment should be permanently discontinued and patient observed until resolution
Grade 4	Permanently discontinue treatment
Transaminases elevation	
Refer to Appendix 9 – Guidance on management of hepatotoxicity for guidance on management of hepatotoxicity	
Neutropenia	
Grade 1 or 2	Continue at the same dose level
Grade 3 or 4, or febrile (any grade)	permanently discontinue treatment
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable Grade 2 Grade ≥ 3	Treat toxicity as clinically appropriate and withhold dose for up to 14 days until toxicity improves to Grade ≤2 • If it does not improve within 14 days of AZD4547 dose interruption, it should be permanently discontinued. • If toxicity improves to Grade <1 reinstate AZD4547 at the current dose maintaining treatment for toxicity as necessary or at lower dose if 2nd occurrence of the same toxicity • If toxicity improves to Grade 2 reinstate AZD4547 at a reduced dose (Dose-1 or dose -2 if recurrence of toxicity) maintaining treatment for toxicity as necessary

Figure 6 : AZD4547 toxicity management guidelines for patients with no visual symptoms of ocular toxicity



Footnotes:

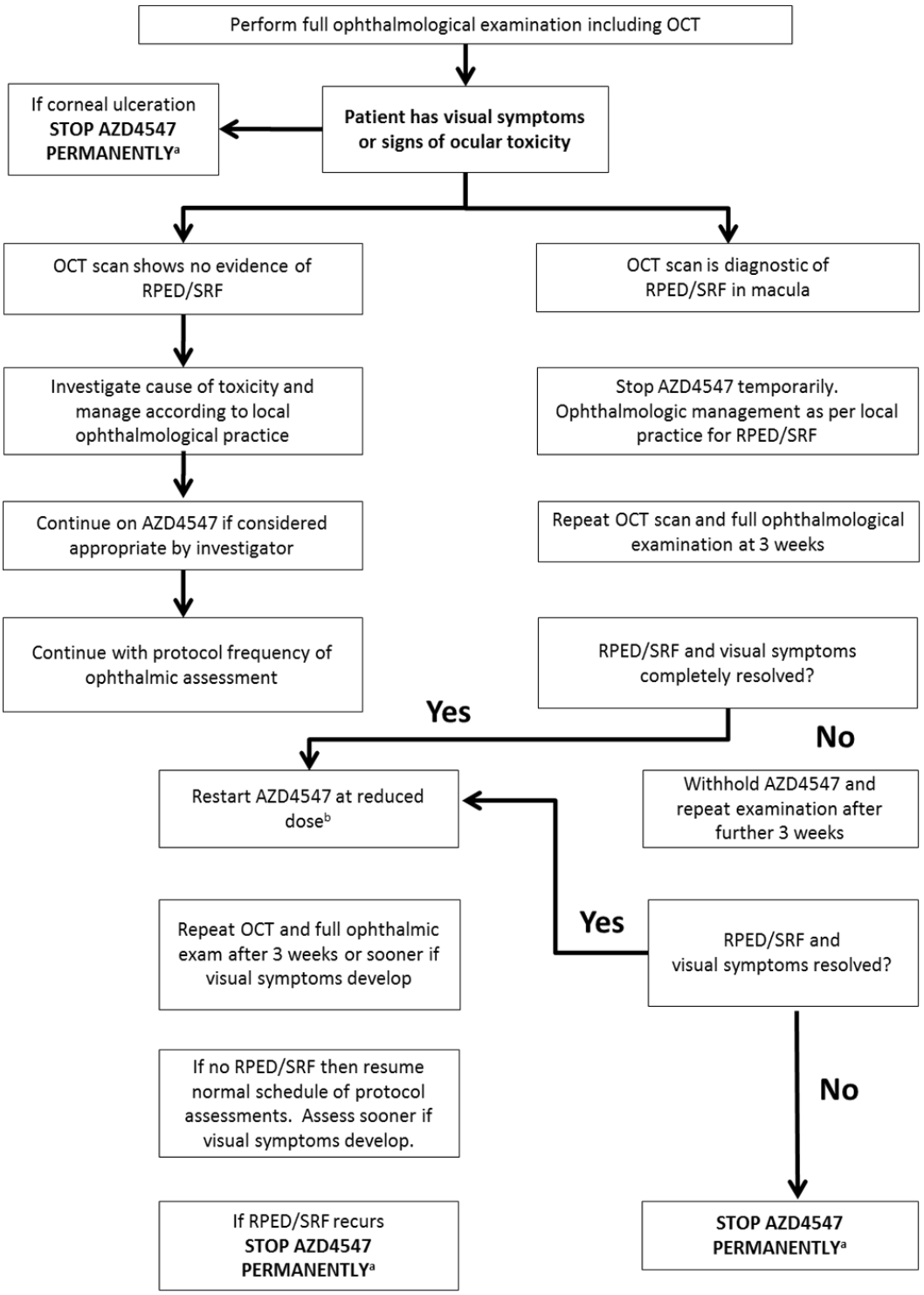
a: Progression of RPED or SRF is defined as development of visual symptoms, extension from para-macular to macula, or increase in the number of lesions.

b: Only 1 dose reduction allowed for management of RPED or SRF.

c: After permanent discontinuation of AZD4547 due to ocular toxicity, patients should be managed according to local clinical practice.

MedDRA Medical Dictionary for Regulatory Activities; OCT Optical-coherence-tomography; RPED or SRF This grouped term includes RPED (MedDRA preferred terms of detachment of retinal pigment epithelium and detachment of macular retinal pigment epithelium), MedDRA preferred term subretinal fluid, MedDRA preferred term serous detachment, MedDRA preferred term retinal detachment (MedDRA lower level term: serous retinal detachment); SRF Subretinal fluid.

Figure 7 : AZD4547 management guidelines for patients with visual symptoms of ocular toxicity



Footnotes:

a: After permanent discontinuation of AZD4547 due to ocular toxicity, patients should be managed according to local clinical practice

b: Only 1 dose reduction allowed for management of RPED or SRF.

MedDRA Medical Dictionary for Regulatory Activities; OCT Optical-coherence-tomography; RPED or SRF This grouped term includes RPED (MedDRA preferred terms of detachment of retinal pigment epithelium and detachment of macular retinal pigment epithelium), MedDRA preferred term subretinal fluid, MedDRA preferred term serous detachment, MedDRA preferred term retinal detachment (MedDRA lower level term: serous retinal detachment); SRF Subretinal fluid

7.6.2.3. AZD5363

Table 7 : AZD5363 management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Diarrhea	
Grade 1 or 2	**Continue at the same dose level, consider introducing supportive therapies and dietetic measures as appropriate**
Grade ≥3 (despite optimal management)	Withhold current dose for up to 28 days until recovery to grade ≤2. Then, resume treatment either at the current dose or at a reduced dose (level -1), upon investigator's judgment. Permanently discontinue treatment if toxicity does not improve after 28 days of treatment interruption
Hyperglycemia	
Grade 1 : FPG < 8.9 mmol/L (160mg/dL)	Continue at the same dose level
Grade 2 : 8.9≤FPG<13.9 mmol/L (160mg/dL-250mg/dL)	If patient is asymptomatic, continue at the same dose level. If patient presents with signs or symptoms*, withhold current dose for up to 28 days and consider appropriate management (refer to section 12.1.3.2 for hyperglycemia guidelines)
Grade 3 : 13.9≤FPG<27.8 mmol/L (250mg/dL-500mg/dL)	If patient is asymptomatic, withhold current dose for up to 28 days and consider appropriate management. If patient presents with signs or symptoms*, withhold current dose for up to 28 days and consider appropriate management. Then monitor FPG as per local guidelines and : • If FPG <8.9mmol/L (160mg/dL) within 48h, resume study treatment at the same dose, and continue treatment for hyperglycemia • If FPG < 8.9mmol/L (160mg/dL) after 48h and before 28 days, resume study treatment at a lower dose, and continue treatment for hyperglycemia • If FPG persists ≥ 8.9mmol/L (160mg/dL), permanently discontinue study treatment within 48h, resume study treatment at the same dose, and continue treatment for hyperglycemia
Grade 4 : FPG>27.8 mmol/L (500mg/dL)	Permanently discontinue treatment
	*polyphagia, polydipsia, polyuria, dizziness, systolic blood pressure <100mmHg, symptoms of ketoacidosis such as breath that smells fruity, nausea, vomiting, mouth extremely dry, short of breath
Cholesterolemia	
Grade 2 : 300<CT<400 mg/dL (7.75-10.34 mmol/L)	Continue at the same dose level
Grade 3 : 400≤CT<500 mg/dL (10.34-12.92 mmol/L)	Reduce treatment to lower dose and consider concomitant management for cholesterolemia
Grade 4 : CT ≥ 500 mg/dl (12.92 mmol/L) despite optimal management of cholesterolemia	Permanently discontinue treatment
QTc prolongation	
Grade 1 : 450-480 ms	Continue at the same dose level

Grade 2 : 481-500 ms	Continue at the same dose level. Assess and correct electrolytes (Ca+, K+, Mg2+) and concomitant medications as appropriate.
Grade 3 : ≥ 501 ms	Withhold AZD5363 until recovery to grade ≤ 1, assess and correct electrolytes (Ca+, K+, Mg2+) and concomitant medications as appropriate, then resume treatment at dose level -1 if AZD5363 related toxicity is suspected. Otherwise, resume at the same dose level (refer to section 12.1.3.5 for ECG surveillance guidelines)
Grade 3 : 1st recurrence or Grade 4 : ≥ 501 ms + 60 ms from baseline and symptoms	Permanently discontinue treatment (refer to section 12.1.3.5 for ECG surveillance guidelines)
LFEV decrease	
Decline of ≥15% and LVEF ≥ 50%	Continue at the same dose level (refer to section 12.1.3.5 for LVEF surveillance guidelines)
Decline of ≥ 10 % and LVEF 49-40%	Continue at the same dose level (refer to section 12.1.3.5 for LVEF surveillance guidelines)
Decline of ≥ 10 % and LVEF < 40%	Withhold investigational drug for up to 28 days. Resume treatment at the same dose level if LVEF returns ≥ 50% (refer to section 12.1.3.5 for LVEF surveillance guidelines). Permanently discontinue treatment if toxicity does not improve after 28 days of treatment interruption or if LVEF drops by a further 10% after investigational drug reintroduction
Transaminase and bilirubin elevation	
Refer to Appendix 9 – Guidance on management of hepatotoxicity for guidance on management of hepatotoxicity	
Skin reaction	
Grade 1 or 2	Continue at the same dose level and initiate dermatological treatment (refer to section 12.1.3.10 for dermatological guidance)
Grade ≥ 3	Withhold investigational drug for up to 28 days until improvement of toxicity with appropriate dermatological treatment (refer to section 12.1.3.10 for dermatological guidance) If toxicity improves to Grade ≤1 within 28 days reinstate AZD5363 at the current dose maintaining supportive therapy. If toxicity improves to Grade 2 within 28 days reinstate AZD5363 at a reduced dose (maximum one dose reduction level is allowed) maintaining supportive therapy If toxicity does not improve to a lower grade within 28 days of AZD5363 interruption, it should be permanently discontinued. Recurrence of a Grade ≥3 : discontinue AZD5363
It is strongly recommended that all patients follow a program of sun-protective measures while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. Refer to section 12.1.3.10 for dermatological guidance.	

Hypersensitivity reactions	
Any grade	Discontinue AZD5363. Symptomatic/supportive therapy should be initiated (including with antihistamines and/or steroids) as considered appropriate by the investigator. Any subsequent decision on rechallenge with AZD5363 at the same or a lower dose, with its potential for recurrence of such or more severe events should be discussed with the sponsor and carefully considered against the potential benefits to the individual patient from continuation of AZD5363 therapy.
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable Grade 2 Grade ≥ 3	Treat toxicity as clinically appropriate and withhold dose for up to 28 days until toxicity improves to Grade ≤2 • If it does not improve within 28 days of AZD5363 dose interruption, AZD5363 should be permanently discontinued. • If toxicity improves to Grade <1 reinstate AZD5363 at the current dose maintaining treatment for toxicity as necessary • If toxicity improves to Grade 2 reinstate AZD5363 at a reduced dose (1 dose level) maintaining treatment for toxicity as necessary

7.6.2.4. AZD8931

Table 8 : AZD8931 management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Ophthalmic toxicities	
Grade 1 or 2	**Continue at the same dose level (or withhold treatment for up to 28 days if intolerable, upon investigator's judgment), manage as appropriate (refer to section 12.1.3.8 for ophthalmic management guidelines)**
Grade ≥3 **Or clinically significant or persistent (ie present for > 7 days**	Withhold current dose for up to 28 days until recovery to grade ≤2 or toxicity becomes tolerable • If toxicity improves to Grade ≤1 within 28 days, reinstate AZD8931 at the current dose maintaining treatment for toxicity as necessary • If toxicity improves to grade 2, reinstate AZD8931 at a reduced dose (dose -1) maintaining treatment for toxicity as necessary. • If toxicity does not improve to a lower grade within 28 days of AZD8931 interruption, it should be permanently discontinued.
LVEF decrease	
Decline of ≥15% and LVEF ≥ 50%	Continue at the same dose level (refer to section 12.1.3.5 for LVEF surveillance guidelines)
Decline of ≥ 10 % and LVEF 49-40%	Continue at the same dose level (refer to section 12.1.3.5 for LVEF surveillance guidelines)
Decline of ≥ 10 % and LVEF < 40%	Withhold investigational drug for up to 28 days. Resume treatment at the same dose level if LVEF returns ≥ 50% (refer to section 12.1.3.5 for LVEF surveillance guidelines). Permanently discontinue treatment if toxicity does not improve after 28 days of treatment interruption or if LVEF drops by a further 10% after investigational drug reintroduction
Diarrhea	
As diarrhoea is a known adverse event that may be caused by AZD8931 it is important that any patient receiving AZD8931 who develops diarrhea should have their electrolytes assessed regularly and any clinically significant electrolyte abnormalities should be corrected with appropriate treatment.	
Grade 1 or 2	Continue at the same dose level, consider introducing supportive therapies and dietetic measures as appropriate
Grade ≥ 3 despite optimal supportive treatment	Withhold current dose for up to 28 days until recovery to grade ≤2. • If toxicity improves to Grade ≤2 within 28 days, or becomes clinically tolerable, reinstate AZD8931 as clinically appropriate, at either the current dose or at a reduced dose (dose -1) maintaining treatment for toxicity as necessary If toxicity does not improve to a lower grade within 28 days of AZD8931 interruption, it should be permanently discontinued.

Pneumonitis/ Interstitial lung disease (not due to disease progression, other pulmonary disease, infection or radiation effect)	
Grade 1	Continue at the same dose level
Grade 2 or 3	1st occurrence: Interrupt dose for up to 28 days until recovery to Grade ≤ 1, then, restart at reduced dose. Permanently discontinue treatment if toxicity fails to recover to grade ≤1 within 28 days. 2nd occurrence: permanently discontinue treatment.
Grade 4	Permanently discontinue treatment
Skin reaction	
Grade 1 or 2	Continue at the same dose level and initiate dermatological treatment (refer to section 12.1.3.10 for dermatological guidance)
Grade ≥ 3 Or clinically significant Or intolerable	Withhold investigational drug for up to 28 days until improvement of toxicity with appropriate dermatological treatment (refer to section 12.1.3.10 for dermatological guidance) If toxicity improves to Grade ≤1 within 28 days reinstate AZD8931 at the current dose maintaining supportive therapy. If toxicity improves to Grade 2 within 28 days reinstate AZD8931 at a reduced dose (dose-1) maintaining supportive therapy If toxicity does not improve to a lower grade within 28 days of AZD8931 interruption, it should be permanently discontinued.
It is strongly recommended that all patients follow a program of sun-protective measures while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. Refer to section 12.1.3.10 for dermatological guidance.	
Stomatitis/ oral mucositis	
Grade 1	Continue at the same dose level
Grade 2 or 3	1st occurrence : withhold current dose for up to 28 days until stomatitis improves to grade ≤ 1, and then resume to the same dose 2nd occurrence : resume treatment at a lower dose. If initial grade 3 reverts to grade ≤ 2 within 28 days, and the patient is showing clinical benefit, treatment may be restarted at the same dose or dose reduced upon investigator judgment. If the toxicity does not resolve to grade ≤ 2 after 28 days, then treatment should be permanently discontinued and patient observed until resolution
Grade 4	Permanently discontinue treatment
QTc prolongation	
Grade 1 : 450-480 ms	Continue at the same dose level
Grade 2 : 481-500 ms	Continue at the same dose level. Assess and correct electrolytes (Ca+, K+, Mg+) and concomitant medications as appropriate.

Grade 3 : ≥ 501 ms	Withhold AZD8931 until recovery to grade ≤ 1, assess and correct electrolytes (Ca+, K+, Mg+) and concomitant medications as appropriate, then resume treatment at dose level -1 if AZD8931 related toxicity is suspected. Otherwise, resume at the same dose level (refer to section 12.1.3.5 for ECG surveillance guidelines)
Grade 3 : 1st recurrence or Grade 4 : ≥ 501 ms + 60 ms from baseline and symptoms	Permanently discontinue treatment (refer to section 12.1.3.5 for ECG surveillance guidelines)
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable grade 2 Or Grade ≥ 3 despite optimal supportive care	Treat toxicity as clinically appropriate and withhold dose for up to 28 days until toxicity improves to Grade ≤2 • If it does not improve within 28 days of AZD8931 dose interruption, AZD8931 should be permanently discontinued. • If toxicity improves to Grade <1 reinstate AZD8931 at the current dose maintaining treatment for toxicity as necessary • If toxicity improves to Grade 2 reinstate AZD8931 at a reduced dose (1 dose level) maintaining treatment for toxicity as necessary

7.6.2.5. Selumetinib

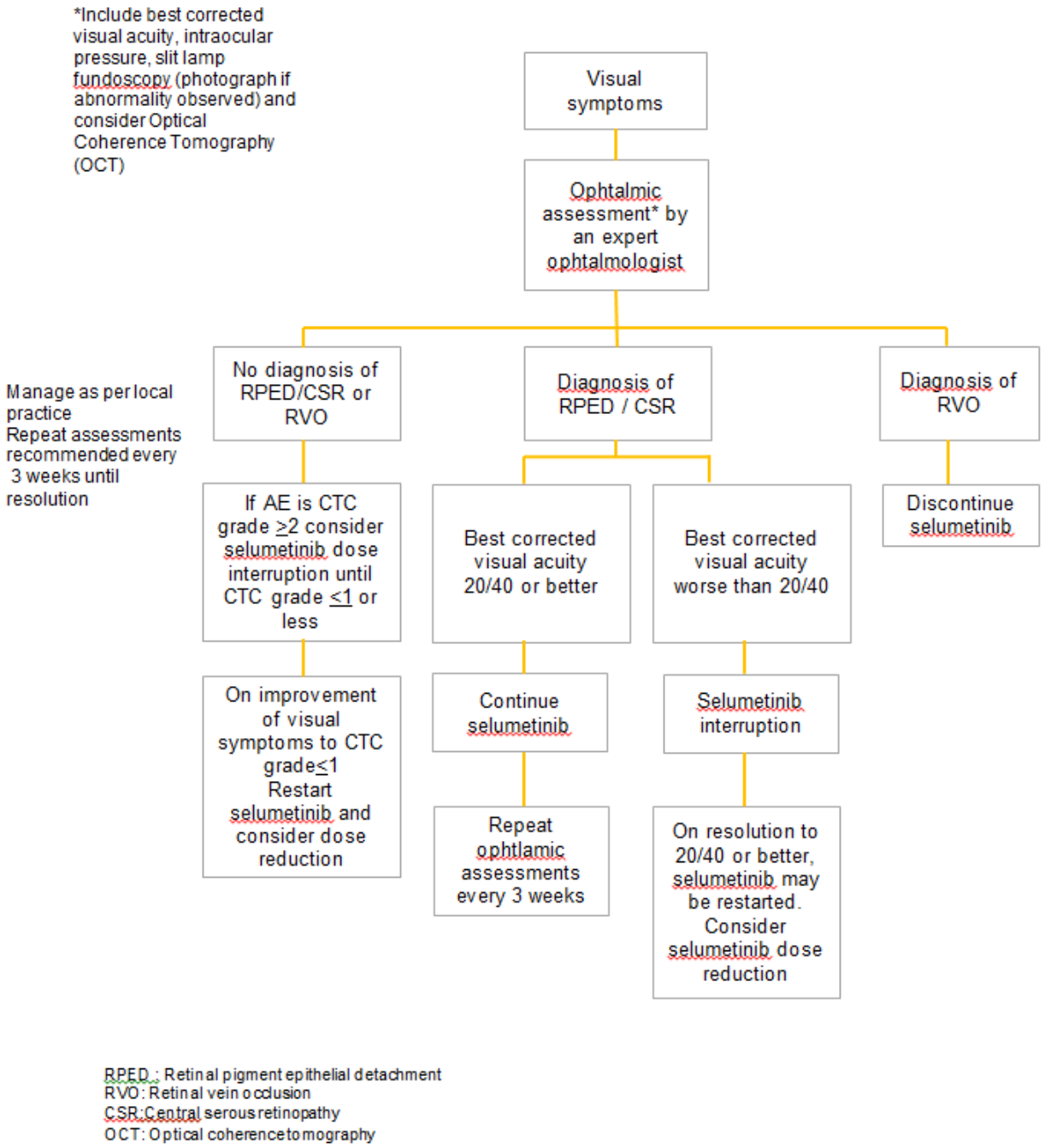
Table 9 : selumetinib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Ophthalmic toxicities	
Grade 1	**Continue at the same dose level, manage as appropriate (refer to section 12.1.3.8 for ophthalmic management guidelines)**
Grade ≥2 **Or clinically significant or persistent (ie present for > 7 days**	Refer to Figure 8: Selumetinib management of eye toxicity for management guidelines
Specific conditions	If diagnosis of retinal vein occlusion is confirmed, treatment should be permanently discontinued
LVEF decrease	
Decline of ≥15% and LVEF ≥ 50%	Continue at the same dose level (refer to section 12.1.3.5 for LVEF surveillance guidelines)
Decline of ≥ 10 % and LVEF 49-40%	Continue at the same dose level (refer to section 12.1.3.5 for LVEF surveillance guidelines)
Decline of ≥ 10 % and LVEF < 40%	Withhold investigational drug for up to 28 days. Resume treatment at the same dose level if LVEF returns ≥ 50% (refer to section 12.1.3.5 for LVEF surveillance guidelines). Permanently discontinue treatment if toxicity does not improve after 28 days of treatment interruption or if LVEF drops by a further 10% after investigational drug reintroduction
Diarrhea	
As diarrhoea is a known adverse event that may be caused by selumetinib it is important that any patient receiving selumetinib who develops diarrhea should have their electrolytes assessed regularly and any clinically significant electrolyte abnormalities should be corrected with appropriate treatment.	
Grade 1 or 2	Continue at the same dose level, consider introducing supportive therapies and dietetic measures as appropriate
Grade ≥ 3 despite optimal supportive treatment	Withhold current dose for up to 28 days until recovery to grade ≤2. • If toxicity improves to Grade ≤2 within 28 days, or becomes clinically tolerable, reinstate selumetinib as clinically appropriate, at either the current dose or at a reduced dose (dose -1) maintaining treatment for toxicity as necessary If toxicity does not improve to a lower grade within 28 days of selumetinib interruption, it should be permanently discontinued
Dyspnea	
New or worsening dyspnea	Refer to Figure 9 : Selumetinib management of patients with new/worsening dyspnoea (not considered related to disease under study) for management guidelines
	If diagnosis of ILD is confirmed, manage as ILD

Pneumonitis/ Interstitial lung disease (not due to disease progression, other pulmonary disease, infection or radiation effect)	
Grade 1	Continue at the same dose level
Grade 2 or 3	1st occurrence: Interrupt dose for up to 28 days until recovery to Grade ≤ 1, then, restart at reduced dose. Permanently discontinue treatment if toxicity fails to recover to grade ≤1 within 28 days. 2nd occurrence: permanently discontinue treatment.
Grade 4	Permanently discontinue treatment
Skin reaction	
Grade 1 or 2	Continue at the same dose level and initiate dermatological treatment (refer to section 12.1.3.10 for dermatological guidance)
Grade ≥ 3 Or clinically significant Or intolerable	Withhold investigational drug for up to 28 days until improvement of toxicity with appropriate dermatological treatment (refer to section 12.1.3.10 for dermatological guidance) If toxicity improves to Grade ≤1 within 28 days reinstate selumetinib at the current dose maintaining supportive therapy. If toxicity improves to Grade 2 within 28 days reinstate selumetinib at a reduced dose (dose-1) maintaining supportive therapy If toxicity does not improve to a lower grade within 28 days of selumetinib interruption, it should be permanently discontinued.
It is strongly recommended that all patients follow a program of sun-protective measures while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. Refer to section 12.1.3.10 for dermatological guidance.	
Stomatitis/ oral mucositis	
Grade 1	Continue at the same dose level
Grade 2 or 3	1st occurrence : withhold current dose for up to 14 days until stomatitis improves to grade ≤ 1, and then resume to the same dose 2nd occurrence : resume treatment at a lower dose. If initial grade 3 reverts to grade ≤ 2 within 14 days, and the patient is showing clinical benefit, treatment may be restarted at the same dose or dose reduced upon investigator judgment. If the toxicity does not resolve to grade ≤ 2 after 14 days, then treatment should be permanently discontinued and patient observed until resolution
Grade 4	Permanently discontinue treatment
Hyperphosphatemia	
If corrected Ca:PO_4 product > 4.5 $mmol^2/l^2$ Or If doubling in PO_4 from baseline	Continue selumetinib at the same dose level and start phosphate chelation therapy as clinically appropriate. If toxicity resolves continue chelation therapy and current selumetinib dose . If toxicity does not resolve before 14 days, continue chelation therapy, reinstate selumetinib at tone dose level lower, except if already at Dose-2 then selumetinib will be permanently discontinued.
Transaminases and /or bilirubin elevation	

Refer to Appendix 9 – Guidance on management of hepatotoxicity for guidance on management of hepatotoxicity	
Serum creatine kinase increased (raised creatine phosphokinase) and possible muscle symptoms	
Refer to Figure 10 : Selumetinib management of patients with creatinine kinase elevation	
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable grade 2 Or Grade ≥ 3 despite optimal supportive care	Treat toxicity as clinically appropriate and withhold dose for up to 28 days until toxicity improves to Grade ≤1 • If toxicity improves to Grade ≤ 1 reinstate selumetinib at the current dose or at a reduced dose at the discretion of the investigator, maintaining treatment for toxicity as necessary • If a further episode of the same toxicity subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the toxicity. • If a different toxicity subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the toxicity. • If it does not improve within 28 days of selumetinib dose interruption, selumetinib should be permanently discontinued

Figure 8: Selumetinib management of eye toxicity



RPED : Retinal pigment epithelial detachment
RVO: Retinal vein occlusion
CSR:Central serous retinopathy
OCT: Optical coherence tomography

Figure 9 : Selumetinib management of patients with new/worsening dyspnoea (not considered related to disease under study)

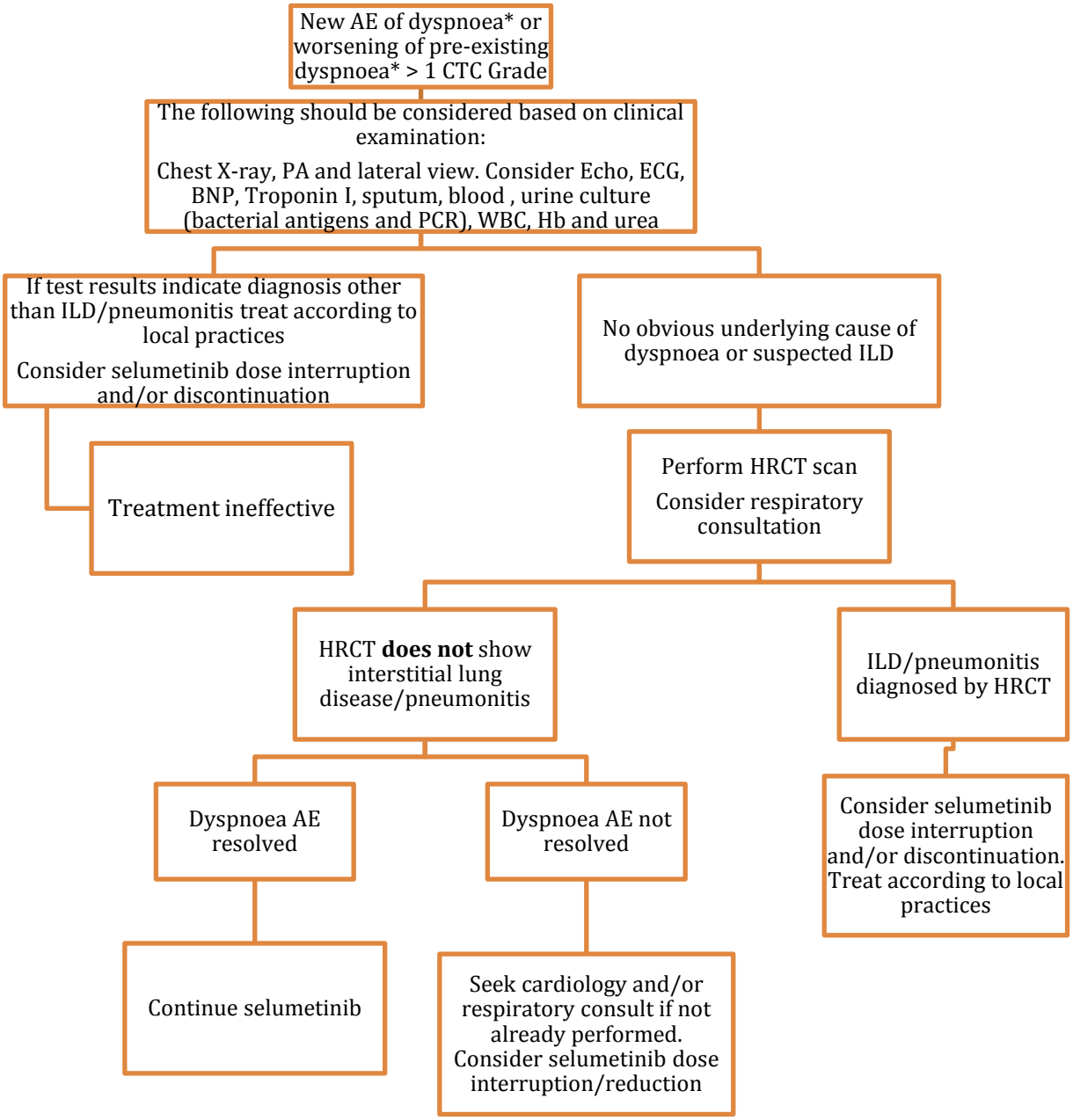
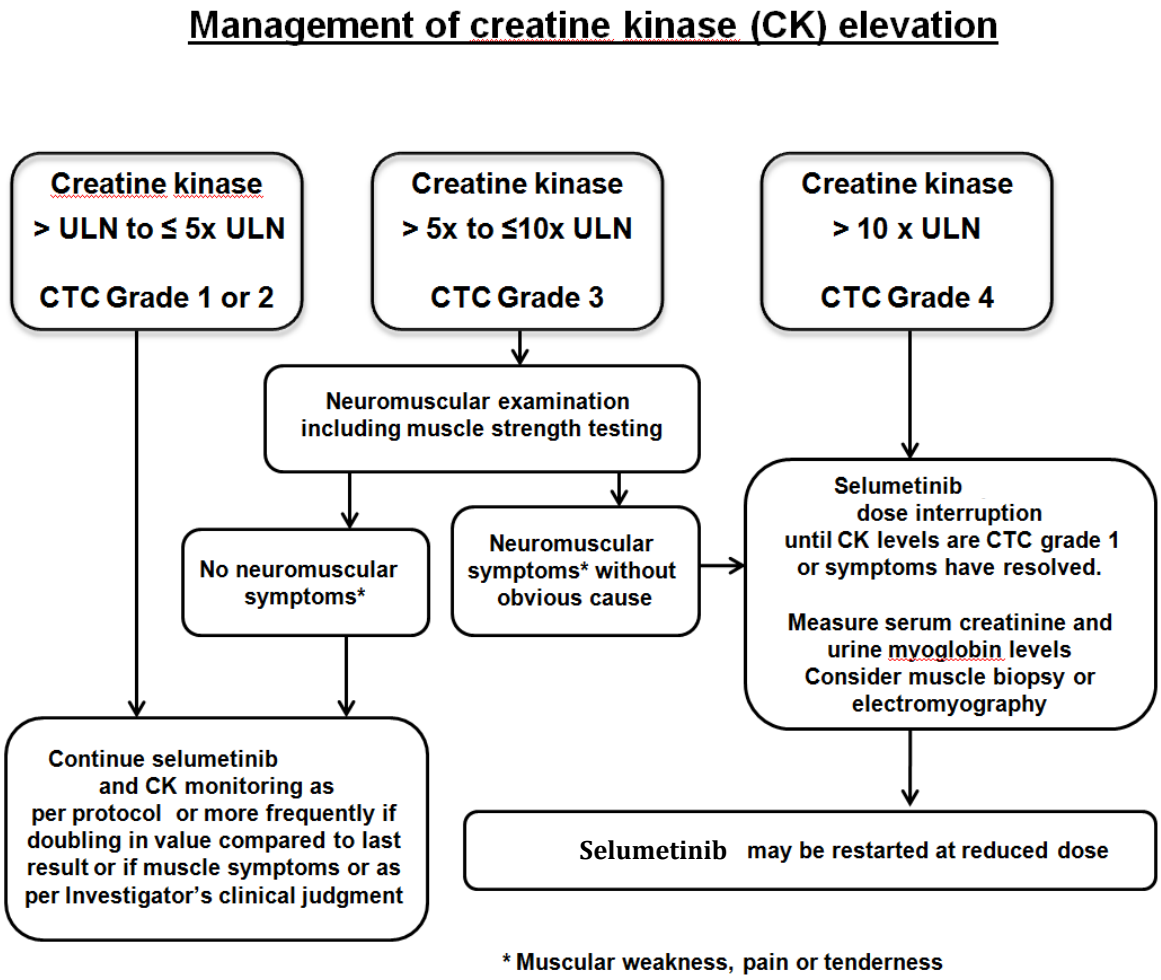


Figure 10 : Selumetinib management of patients with creatinine kinase elevation



7.6.2.6. Vandetanib

Table 10 : Vandetanib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Diarrhea	
Grade 1 or 2	**Continue at the same dose level, consider introducing supportive therapies and dietetic measures as appropriate**
Grade ≥3 (despite optimal management)	Withhold current dose for up to 21 days until recovery to grade ≤1. Then, resume treatment at a reduced dose (level -1). Permanently discontinue treatment if toxicity does not improve after 21 days of treatment interruption If grade ≥3 toxicity recurs after dose reduction, permanently discontinue treatment
Electrolyte supplementation with regular laboratory monitoring should be used to maintain electrolytes within normal limits and to prevent an increased risk of QTc prolongation	
Skin reaction	
Grade 1 or 2	Continue at the same dose level and initiate dermatological treatment*
Grade ≥ 3 Or clinically significant Or intolerable	Withhold investigational drug for up to 21 days until improvement of toxicity with appropriate dermatological treatment* (refer to section 12.1.3.10 for dermatological guidance) If toxicity improves to Grade ≤1 within 21 days reinstate vandetanib at a reduced dose (level-1) maintaining supportive therapy*. Permanently discontinue treatment if toxicity does not improve after 21 days of treatment interruption If grade ≥3 toxicity recurs after dose reduction, permanently discontinue treatment
* It is strongly recommended that all patients follow a program of sun-protective measures while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. Refer to section 12.1.3.10 for dermatological guidance	
QTc prolongation	
Grade 1 : 450-480 ms	Continue at the same dose level
Grade 2 : 481-500 ms	Continue at the same dose level. Assess and correct electrolytes (Ca+, K+, Mg2+) and concomitant medications as appropriate.
Grade 3 : ≥ 501 ms	Withhold vandetanib until recovery to grade ≤ 1, assess and correct electrolytes (Ca+, K+, Mg2+) and concomitant medications as appropriate, then resume treatment at dose level -1 if vandetanib related toxicity is suspected. Otherwise, resume at the same dose level (refer to section 12.1.3.5 for ECG surveillance guidelines)
Grade 3 : 1st recurrence or Grade 4 : ≥ 501 ms + 60 ms from baseline and symptoms	Permanently discontinue treatment (refer to section 12.1.3.5 for ECG surveillance guidelines)
Specific conditions	if patient develops Torsade de Pointes or ventricular tachycardia, withhold investigational drug. It can be resumed at a lower dose when the arrhythmia has resolved and the ECG QT has returned to normal.

Hypertension	
Grade 1 or 2	Continue at the same dose level and consider appropriate medication at grade 2
Grade 3	Continue at the same dose level if blood pressure is controlled on increased anti-hypertensive medication and returns to grade ≤ 1 or baseline level. If blood pressure cannot be stabilized with increased anti-hypertensive medication, study treatment must be withheld and cannot be resumed until blood pressure is controlled to baseline level. Upon recovery, the treatment will be resumed at a permanently reduced dose.
Grade 4	Withhold investigational drug and resume therapy only when blood pressure is controlled to baseline level. Upon recovery, the treatment will be resumed at a permanently reduced dose.
Transaminase and/or bilirubin elevation	
Refer to Appendix 9 – Guidance on management of hepatotoxicity for guidance on management of hepatotoxicity	
Pneumonitis/ Interstitial lung disease (not due to disease progression, other pulmonary disease, infection or radiation effect)	
Grade 1	Continue at the same dose level
Grade 2 or 3	1st occurrence: Interrupt dose for up to 28 days until recovery to Grade ≤ 1, then, restart at reduced dose. Permanently discontinue treatment if toxicity fails to recover to grade ≤1 within 28 days. 2nd occurrence: permanently discontinue treatment
Grade 4	Permanently discontinue treatment
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable Grade 2 Grade ≥ 3	Treat toxicity as clinically appropriate and withhold dose for up to 28 days until toxicity improves to Grade ≤2 • If it does not improve within 28 days of vandetanib dose interruption, vandetanib should be permanently discontinued. • If toxicity improves to Grade <1 reinstate vandetanib at the current dose maintaining treatment for toxicity as necessary • If toxicity improves to Grade 2 reinstate vandetanib at a reduced dose (1 dose level) maintaining treatment for toxicity as necessary
Posterior reversible encephalopathy syndrome, PRES (posterior leukoencephalopathy syndrome-RPLS)	
First occurrence	Permanently discontinue treatment

7.6.2.7. Olaparib

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with Unicancer.
All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.
Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.
Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.
Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 11 : Olaparib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once dose is reduced, escalation is not permitted.	
Anaemia Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence).	
Hb < 10 but ≥ 8 g/dl (CTCAE Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg transfusion) or interrupt dose for a maximum of 4 weeks. If repeat Hb< 10 but ≥ 8 g/dl, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to 250 mg twice daily as a first step and to 200 mg twice daily as a second step may be considered.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks. until improved to Hb ≥ 10 g/dl. Upon recovery dose reduce to 250 mg twice daily as a first step and to 200 mg twice daily as a second step in the case of repeat Hb decrease.

Neutropenia, leucopenia and thrombocytopenia Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary. Platelet transfusions, if indicated, should be done according to local hospital guidelines. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse).	
Grade 1 or 2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation.
Grade 3 or 4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg twice daily as a first step and 200 mg twice daily as a second step.
Management of prolonged haematological toxicities	
	If a patient develops prolonged haematological toxicity such as: • ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence • ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 109/L) • ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 109/L) Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.
Management of non hematological toxicities	
Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment. Study treatment can be dose reduced to 250 mg bd as a first step and to 200 mg bd as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.	
New or worsening pulmonary symptoms (e.g, Dyspnea)	

New or worsening pulmonary symptoms (e.g.dyspnea) or radiological abnormality	Refer to Figure 9 : Selumetinib management of patients with new/worsening dyspnoea (not considered related to disease under study) for management guidelines as for selumetinib
	If significant pulmonary abnormalities are identified, refer to guidelines for pulmonary toxicities.
Nausea and vomiting Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months. No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie 2 pieces of toast or a couple of biscuits). As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines or dexamethasone.	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable Grade 2 Grade ≥ 3	Treat toxicity as clinically appropriate and withhold dose for up to 14 days until toxicity improves to Grade ≤2 • If it does not improve within 14 days of dose interruption, it should be permanently discontinued. • If toxicity improves to Grade <1 reinstate olaparib at the current dose maintaining treatment for toxicity as necessary
Other toxicities	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level. Consider introducing supportive therapies or concomitant medications if appropriate
Intolerable Grade 2 Grade ≥ 3	Treat toxicity as clinically appropriate and withhold dose for up to 14 days until toxicity improves to Grade ≤2 • If it does not improve within 14 days of olaparib dose interruption, it should be permanently discontinued. • If toxicity improves to Grade <1 reinstate olaparib at the current dose maintaining treatment for toxicity as necessary or at lower dose if 2nd occurrence of the same toxicity • If toxicity improves to Grade 2 reinstate olaparib at a reduced dose (Dose-1 or dose -2 if recurrence of toxicity) maintaining treatment for toxicity as necessary
Renal Impairment	
Calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min	A dose reduction is recommended for patients who develop moderate renal impairment for any reason during the course of the study: the dose of olaparib should be reduced to 200mg BD.
Creatinine clearance ≤ 30 ml/min	Olaparib has not been studied in patients with severe renal impairment or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

7.6.2.8. Savolitinib

Table 12 : Savolitinib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Non-hepatic study drug-related toxicity	
Grade 0, 1, or 2	**None**
Grade 3 (despite appropriate supportive care)	**Hold dosing and follow algorithm bellow:** • Grade 3 toxicity for ≤7 days and resolves to ≤Grade 1 or baseline : Resume dosing at one reduced dose level (maximum of 2 dose reductions) • Grade 3 toxicity for >7 days: Discontinue study drug
Recurrence of Grade 3	• Grade 3 toxicity for ≤7 days and resolves to ≤Grade 1 or baseline : Resume dosing at one reduced dose level (maximum of 2 dose reductions) • Grade 3 toxicity for >7 days: Discontinue study drug
Recurrence of Grade 4	**Discontinue study drug**
Special interest situation:	
Dermatologic	A case of Stevens-Johnson syndrome (SJS) has been reported in temporal association with savolitinib. Patients who show symptoms or signs suggesting emerging Stevens-Johnson syndrome (SJS) while on study treatment (e.g., progressive skin rash often with blisters or mucosal lesions), must discontinue savolitinib immediately and receive appropriate treatment. If emerging SJS is suspected, re-challenge with savolitinib must be avoided.
Hypersensitivity:	Hypersensitivity, which may manifest as drug eruption, hypotension or myalgia has been reported after savolitinib dosing. Patients who show symptoms of suspected savolitinib-related hypersensitivity must follow the dose modifications for non-hepatic study drug-related toxicities. Dosing with savolitinib can resume only after consultation with the study physician
Pyrexia:	If fever occurs savolitinib must be interrupted until aetiology is established after thorough investigation. In cases where fever is considered causally related to savolitinib, then savolitinib must be discontinued.
Hepatic study drug-related toxicity	
1. Discontinue drug if – ALT or AST >8x ULN, or – ALT or AST >5xULN for >2 weeks, or – ALT or AST >3xULN and (TB>2xULN or INR>1.5 if not on anticoagulants that elevate the INR) – AST or ALT >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5% 2. Withhold dosing if ALT or AST > 5-8xULN without TB elevation above baseline or ULN, repeat LFT testing twice a week for 1 week; – If improved to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks; – If not, discontinue	

3. Withhold dosing if ALT or AST >3xULN and concurrent TB 1.5~2xULN, repeat LFT testing twice a week for 1 week,
– If both ALT/AST and TB improved to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks
– If not, discontinue
4. Continue dosing if ALT or AST >3 -5xULN without TB elevation above baseline or ULN, repeat LFT testing every week
– If ALT or AST trending upward, withhold dosing and repeat LFT twice a week for 1 week;
– if improve to grade 1 or baseline in 1 week, resume at same dose with LFT testing every week for 6 weeks
– if improve to grade 1 or baseline in 2 weeks, resume at reduced dose with LFT testing every week for 6 weeks
– If not, discontinue
5. Discontinue for recurrent ALT or AST >5xULN
6. Discontinue for recurrent ALT or AST >3-5xULN and TB >1.5~2xULN
7. Withhold dosing for recurrent ALT or AST >3-5xULN without TB elevation above baseline or ULN, repeat LFT testing twice a week for 1 week
– if improve to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing every week for 6 weeks; if not, discontinue

7.6.2.9. Vemurafenib

Table 13 : Vemurafenib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Any Adverse Events	
Grade 1 or Grade 2 (tolerable)	**Maintain vemurafenib at a dose of 960 mg twice daily.**
Grade 2 (intolerable) or Grade 3	1st occurrence of any grade 2 or 3 AE : Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered). 2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption: Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily). 3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction: Discontinue permanently.
Grade 4	1st occurrence of any grade 4 AE: Discontinue permanently or interrupt Vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily). 2nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction: Discontinue permanently.
Cutaneous toxicities	
Cutaneous Squamous Cell Carcinoma (cuSCC):	If treatment is continued, it is recommended to do it without modifying the dose of vemurafenib.
Severe dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis:	**Discontinue permanently. (Refer to section 12.1.3.14 for cuSCC surveillance guidelines).**
Hypersensitivity reactions	
Severe hypersensitivity reactions including generalized rash and erythema or hypotension:	Discontinue permanently.
Prolongation of the QT interval	
QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values	Discontinue permanently.
1st occurrence of QTc>500 ms during treatment	Temporarily interrupt treatment until QTc decreases below 500 ms.

and change from pre-treatment value remains <60 ms	Assess and correct electrolytes (K+, Mg++, and Ca++) and concomitant medications as appropriate. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered). Refer to section 12.1.3.5 for ECG surveillance guidelines.
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Assess and correct electrolytes (K+, Mg++, and Ca++) and concomitant medications as appropriate.Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily). Refer to section 12.1.3.5 for ECG surveillance guidelines.
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60 ms	Discontinue permanently.

7.6.2.10. Cobimetinib

Table 14 : cobimetinib management guidelines and dose modifications

ADVERSE REACTION	MANAGEMENT GUIDELINES AND DOSE MODIFICATION ALGORITHMS
Any Adverse Events includind serous retinopathy	
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at a dose of 60 mg once daily (3 tablets)
Grade 2 (intolerable) or Grade 3/4	1st occurrence : Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg once daily (2 tablets) 2nd occurrence : Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg once daily (1 tablet) 3rd occurrence: Consider permanent discontinuation.
Left ventricular dysfunction	
	Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption.
Patient asymptomatic LVEF value : ≥ 50% (or 40-49% and < 10% absolute decrease from baseline)	Continue at current dose
Patient asymptomatic LVEF value : < 40% (or 40-49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks: If LVEF value following treatment break is : - < 10% absolute decrease from baseline: • 1st occurrence: 40 mg • 2nd occurrence: 20 mg • 3rd occurrence: permanent discontinuation -< 40% (or ≥ 10% absolute decrease from baseline): Permanent discontinuation
Patient symptomatic	Interrupt treatment for 4 weeks If LVEF value following treatment break is : - asymptomatic and < 10% absolute decrease from baseline • 1st occurrence: 40 mg • 2nd occurrence: 20 mg • 3rd occurrence: permanent discontinuation -asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline) : Permanent discontinuation -symptomatic regardless of LVEF: Permanent discontinuation
Rhabdomyolysis or CPK elevations	

Rhabdomyolysis or symptomatic CPK elevations	Interrupt cobimetinib treatment. If severity is improved by at least on grade within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when cobimetinib treatment is modified, if clinically indicated. If rhabdomyolysis or symptomatic CPK elevation do not improve within 4 weeks, permanently discontinue cobimetinib treatment.
Asymptomatic CPK elevations: Grade ≤ 3	Cobimetinib dosing does not need to modified or interrupted to manage asymptomatic Grade ≤ 3 CPK elevations.
Asymptomatic CPK elevations: Grade 4	Interrupt cobimetinib treatment. If improved to Grade ≤ 3 within 4 weeks, restart Cotellic at a dose reduced by 20
Hemorrhage	
Grade 3 events	Interrupt Cotellic treatment. There is no data on the effectiveness of Cotellic dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting Cotellic treatment. Zelboraf dosing can be continued when Cotellic treatment is interrupted, if clinically indicated.
Grade 4 events or cerebral hemorrhage (all grades)	Interrupt Cotellic treatment. Permanently discontinue Cotellic for hemorrhage events attributed to Cotellic.
Dose modification advice for Cotellic when used with vemurafenib	
Liver laboratory abnormalities	
Grade 1 and 2	Cobimetinib and vemurafenib should be continued at the prescribed dose.
Grade 3	Cobimetinib should be continued at the prescribed dose. The dose of vemurafenib may be reduced as clinically appropriate. Please refer to the vemurafenib SmPC.
Grade 4	Cotbimetinib treatment and vemurafenib treatment should be interrupted. If liver laboratory abnormalities improve to Grade ≤1 within 4 weeks, Cobimetinibshould be restarted at a dose reduced by 20 mg and vemurafenib at a clinically appropriate dose, per its SmPC. Cobimetinib treatment and vemurafenib treatment should be discontinued if liver laboratory abnormalities do not resolve to Grade ≤1 within 4 weeks or if Grade 4 liver laboratory abnormalities recur after initial improvement.
Photosensitivity	
Grade ≤2 (tolerable)	Photosensitivity should be managed with supportive care.
Grade 2 (intolerable) or Grade ≥3	Cobimetinib and vemurafenib should be interrupted until resolution to Grade ≤1. Treatment can be restarted with no change in cobimetinib dose. Vemurafenib dosing should be reduced as clinically appropriate, please refer to its SmPC for further information.
Rash **Rash events may occur with either Cotellic or vemurafenib treatment. The dose of Cotellic and/or vemurafenib may be either temporarily interrupted and/or**	

reduced as clinically indicated. **Additionally, for:**	
Grade ≤2 (tolerable)	Rash should be managed with supportive care. Cobimetinib dosing can be continued without modification.
Grade 2 (intolerable) or Grade ≥3 acneiform rash	General dose modification recommendations for cobimetinib should be followed. Vemurafenib dosing can be continued when cobimetinib treatment is modified (if clinically indicated).
Grade 2 (intolerable) or Grade ≥3 non-acneiform or maculopapular rash	Cobimetinib dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced, please refer to its SmPC for further information.
QT prolongation	
If during treatment the QTc exceeds 500 msec, please refer to the vemurafenib management guidelines and dose modifications. No dose modification of cobimetinib is required when taken in combination with vemurafenib.	
For new or worsening visual disturbances (chorioretinopathy or retinal detachment for example).	
If symptoms of new or worsening visual disturbances are identified, an ophthalmologic examination is recommended. If serous retinopathy is diagnosed, Cotellic treatment should be withheld until visual symptoms improve to Grade ≤1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation	

7.6.2.11. Durvalumab (MEDI4736)

For adverse events (AEs) that are considered at least partly due to administration of durvalumab the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (see below).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (see Table 15 : Durvalumab management guidelines and dose modifications). **Dose reductions are not permitted.**
Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.
Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in
Table 15.
In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 12.1.3.16.

Table 15 : Durvalumab management guidelines and dose modifications

PART 1 : DOSING MODIFICATIONS AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED REACTIONS ASSOCIATED WITH -DURVALUMAB		
ADVERSE REACTION	**DOSE MODIFICATIONS**	**TOXICITY MANAGEMENT**
Immune-related Adverse Events (Overall Management)		
Grade 1	No dose modification	**It is recommended that management of immune-mediated adverse event follow the guidelines presented in this table** - It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. - Whether specific immune-mediated events (and/or laboratory indicators of such events)events are noted in these guidelines or not, subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) to a possible immune-mediated event. - In the absence of a clear alternative etiology, all events should be managed as if they were immune related. General recommendations follow. - Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events - For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3)
Grade 2	Hold study drug dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent.	

Grade 3	Depending on the individual toxicity, may permanently discontinue study drug. Please refer to guidelines below	events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. - If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). - More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the immune-mediated adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. - With long-term steroid and other immunosuppressive use, consider need for Pneumocystispneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystispneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. - Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.
Grade 4	Permanently discontinue study drug Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug, and if complete work up shows no evidence of pancreatitis, study drug may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	

Pneumonitis / ILD		
Any grade	General Guidance	- Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below - Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
Grade 1 Radiographic changes only (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modification required. However, consider holding study drug dosing as clinically appropriate and during diagnostic work-up for other etiologies	- Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
Grade 2 Mild to moderate new symptoms (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	- Monitor symptoms daily and consider hospitalization - Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). - Reimaging as clinically indicated - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to4mg/kg/day started. - If still no improvement within 3 to 5 days, despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation). - Consider pulmonary and infectious disease consult. - Consider, as necessary, discussing with study physician.

Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug.	- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. - Obtain pulmonary and infectious disease consult, consider, as necessary, discussing with study physician. - Hospitalize the patient - Supportive Care (oxygen, etc.) - If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Once the patients is improving, gradually taper steroids over ≥28 and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).
Diarrhea/Colitis		
Any grade	General Guidance	- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). - Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections, etc.) - Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event - Use analgesics carefully; they can mask symptoms of perforation and peritonitis
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis:	No dose modification	Monitor closely for worsening symptoms Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.

asymptomatic; clinical or diagnostic observations only)		
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	Hold study drug until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤ then study drug can be resumed after completion of steroid taper.	- Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. - If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab - Consider, as necessary, discussing with study physician if no resolution to ≤ Grade 1 in 3 to 4 days - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical	Grade 3 Permanently discontinue study drug for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. Grade 4 Permanently discontinue study drug/study regimen.	- Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. - Monitor stool frequency and volume and maintain hydration - Urgent GI consult and imaging and/or colonoscopy as appropriate - If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)		
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**		
Any grade		Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	No dose modification If it worsens, treat as Grade 2 event	Continue LFT monitoring per protocol
Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	Hold Study drug dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to Grade ≤1 or baseline, resume study drug after completion of steroid taper.	-Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. - Discuss with study physician if no resolution to ≤ Grade 1 in 1-2 days. If event is persistent (> 3 to5 days) or worsens, promptly start prednisone 1-to 2 mg/kg/day PO or IV equivalent. - If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2-4mg/kg/day - If still no improvement within 3 to5 days, despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	For Grade 3: For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug dose until resolution to Grade ≤1 or baseline • Resume study drug if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug. Permanently discontinue study drug for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.b For Grade 4:Permanently discontinue study drug	- Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. -If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. - Perform hepatology consult, abdominal workup, and imaging as appropriate.-Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune-related hepatitis.** **THIS shaded area is guidance only for management of "Hepatitis (elevated LFTs)" in HCC patients** **See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation**		
Any grade	General Guidance	For Any Grade: – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold

		For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation	
Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	For Grade 2: – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).a Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used.
Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly

(Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.b	initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).a
Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	Same as above (except would recommend obtaining liver biopsy early)
Nephritis or renal dysfunction (elevated serum creatinine)		
Any grade	General Guidance	- Consult with nephrologist. - Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). - Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). - Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	- Monitor serum creatinine weekly and any accompanying symptoms. - If creatinine returns to baseline, resume its regular monitoring per study protocol. - If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. - Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.

Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug until resolution to ≤1 or baseline. If toxicity worsens, then treat as Grade 3 or 4. If toxicity improves to Grade ≤1 or baseline, then resume study drug after completion of steroid taper.	- Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. - Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. - Consult nephrologist and consider renal biopsy if clinically indicated. - If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment - When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug.	- Carefully monitor serum creatinine on daily basis. - Consult nephrologist and consider renal biopsy if clinically indicated. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment.
Rash (excluding bullous slkin formations)		
Any grade	General Guidance (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	- Monitor for signs and symptoms of dermatitis (rash and pruritus) - IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED.
Grade 1	No dose modification	- Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to Grade ≤1 or baseline after completion	- Obtain dermatology consult. Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)

	of steroid taper.	- Consider moderate-strength topical steroid - If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening, despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start IV equivalent. - Consider systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent - Consider skin biopsy if the event ispersistent for >1 to 2 weeks or recurs
Grade 3	- Hold study drug until resolution to ≤ Grade 1 or baseline - If temporarily holding the study drug does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug	- Consult dermatology Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/dayor equivalent - Consider hospitalization - Monitor extent of rash [Rule of Nines] - Consider skin biopsy (preferably more than 1) as clinically feasible. - Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). - Discuss with study physician
Grade 4	Permanently discontinue study drug	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency, pancreatitis, , exocrine event of amylase/lipase increased also included in this section)		
Any grade (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	- Consider consulting an endocrinologist for endocrine events. - Consider, as necessary, discussing with study physician. - Monitor subjects for signs and symptoms of endocrinopathies. Nonspecific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, polydipsia, polyuria and weakness. - Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) - Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). - For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other

		signs or symptoms of pancreatic inflammation. - If a subject experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
Grade 1 including those with asymptomatic TSH elevation	No dose modification	- Monitor patient with appropriate endocrine function tests - For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). - If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
Grade 2 including those with symptomatic endocrinopathy	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, Hold study drug dose until patient is clinically stable. • If worsens then treat as Grade 3 or Grade 4 t • Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. Doses of prednisone are ≤10 mg/day or equivalent.	- Consult endocrinologist to guide evaluation of endocrine function, and as indicated by suspected endocrinopathy endocrine function, and as clinically indicated, consider pituitary scan - For subjects with abnormal endocrine work up, except for those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term, high-dose corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones) - Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. - Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. - Once the patient on steroids is improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). - For subjects with normal endocrine work up (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug dose until	

	endocrinopathy symptom(s) are controlled - Study drug can be resumed once event stabilizes and after completion of steroid taper	- Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended.
Grade 4	Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per investigator or treating physician's clinical judgement. Doses of prednisone are ≤10 mg/day or equivalent.	- - For all patients with abnormal endocrine work up, except those with isolated hypothyroidism, Type 1 DM, and as guided by an endocrinologist, . - Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent as well as relevant. -Administer hormone replacement (e.g., hydrocortisone, sex hormones). - For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity - Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. - Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. - Once patient on steroids is improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for tre atment of cancer-related infections [Category 2B recommendation]).
Immune mediated Neurotoxicity (except Myasthenia Gravis and Guillain-Barre)		
Any grade (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	- Subjects should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) - Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) - Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) - Symptomatic treatment with neurological consult as appropriate
Grade 1	No dose modification	See "Any Grade" recommendations above.
Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug dose until resolution to ≤ Grade 1	- Discuss with the study physician - Obtain Neurology Consult - Sensory neuropathy/neuropathic pain may be managed by appropriate

	• For sensory neuropathy/neuropathic pain, consider holding study drug dose until resolution to ≤ Grade 1. o If toxicity worsens then treat as Grade 3 or Grade 4 Study drug can be resumed once event improves to Grade ≤1 and after completion of steroid taper.–	medications (e.g., gabapentin, duloxetine, etc.) - Promptly start systemic steroids prednisone 1 to 2mg/kg/day PO or IV equivalent - If no improvement within 3 to 5 days, despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIgG)
Grade 3	• Hold Study drug dose until resolution to ≤ Grade 1 • Permanently discontinue Study drug if Grade 3 or AE does not resolve to ≤ Grade 1 within 30 days.	- Discuss with study physician - ObtainNeurology Consult - Consider hospitalization - Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent - If no improvement , within 3 to 5 days, despite IV corticosteroids consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIgG) - Once stable, gradually taper steroids over ≥28 days
Grade 4	Permanently discontinue study drug	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		
Any grade	General Guidance	- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability - Subjects should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult - Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation - It Is important to consider that the use of steroids as the primary

		treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG
Grade 1	No dose modification	- Discuss with the study physician - Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above - Obtain a neurology consult unless the symptoms are very minor and stable
Grade 2	- Hold study drug dose until resolution to ≤ Grade 1 - Permanently discontinue study drug if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	- Discuss with the study physician - Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above - Obtain a Neurology Consult - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) MYASTHENIA GRAVIS: o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIgG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: • Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative). • Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 Severe	- Hold study drug dose until resolution to ≤ Grade 1 - Permanently discontinue Study drug if Grade 3 immune-mediated adverse event does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	- Discuss with study physician - Recommend hospitalization - Monitor symptoms and obtain neurological consult MYASTHENIA GRAVIS:

Grade 4 Life threatening	Permanently discontinue study drug	o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: • Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. • Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis		
Any grade	General Guidance Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	– The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
Grade 1 (asymptomatic	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during	- Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry

with laboratory (e.g., BNP) or cardiac imaging abnormalities)	diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	(resting and exertion), and laboratory work-up as clinically indicated. Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	– Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolonemethylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).a
Myositis/Polymyositis ("Poly/myositis")		
Any grade	General Guidance	– Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing

		stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	– Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	- Monitor symptoms daily and consider hospitalization. - Obtain Neurology consult, and initiate evaluation. - Consider, as necessary, discussing with the study physician. - If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant - If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start

		treatment with IV methylprednisolone 2 to 4 mg/kg/day - If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	For Grade 3: Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. For Grade 4: - Permanently discontinue study drug/study regimen.	- Monitor symptoms closely; recommend hospitalization. - Obtain Neurology consult, and complete full evaluation. - Consider, as necessary, discussing with the study physician. - Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. - If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. - Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
PART 2 : DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR INFUSION-RELATED REACTIONS ASSOCIATED WITH –DURVALUMAB		
Infusion- related reactions		
Any grade	General Guidance	- Management per institutional standard at the discretion of investigator - Monitor subjects for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	- The infusion rate of study drug may be decreased by 50% or temporarily interrupted until resolution of the event	- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator - Consider premedication per institutional standard prior to subsequent doses - Steroids should not be used for routine premedication of Grade ≤2

		infusion reactions.
Grade 2	- The infusion rate of study drug may be decreased 50% or temporarily interrupted until resolution of the event (up to 4 hours) - Subsequent infusions may be given at 50% of the initial infusion rate	Same as grade 1
Grade 3/ 4	Permanently discontinue study drug	Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)
PART 3 : DOSE MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR NON-IMMUNE MEDIATED REACTIONS ASSOCIATED WITH -DURVALUMAB		
Any grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
Grade 1	No dose adjustment	Treat accordingly as per institutional standard
Grade 2	Hold study drug until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
Grade 3	Hold study drug until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug administration at next scheduled dose. Otherwise, discontinue study drug	Treat accordingly as per institutional standard
Grade 4	Discontinue Study drug (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

Table 16: Summary table for study drug dose, reductions and schedule

Study drug	Vistusertib	AZD4547	AZD5363	AZD8931	Selumetinib	Vandetanib	Olaparib	Savolitinib	Vemurafenib + Cobimetinib		MEDI4736
									Vemurafenib	Cobimetinib	
Starting Dose	50 mg bd	80 mg bd	480 mg bd	40 mg bd	75 mg bd	300 mg od	300 mg bd	600 mg od (400 mg od for patient with body weight less than 50 kg)	960 mg bd,	60 mg od,	10 mg/kg
Reduced Dose –1	35 mg bd	60 mg bd	400 md bd	20 mg bd	75 mg od	200 mg od	250 mg bd	400 mg od	720 mg bd	40 mg od	
Reduced Dose –2	25 mg bd	40 mg bd	320 mg bd		50 mg bd	100 mg od	200 mg bd	200 mg od	480 mg bd	20 mg od	
Reduced Dose –3					50 mg od	100 mg every other day					

Schedule	Continuous	2 weeks on -1 week off	4 days on -3 days off	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous	21 days on / 7 days off	Every 2 weeks

Standard maintenance drugs should be administered and dose reduced according to Summary of Product Characteristics recommendations and local standard practice.

NOTE: Schedule should remain the same, only dose changes.

7.7. Concomitant medications, non-drug therapies and interactions

7.7.1. Reporting guidelines

All medications that may interact with one of the study drugs or may induce or potentiate some study drugs related adverse events should be reported on the concomitant treatment form of the study CRF, if they were taken within 14 days (or before for specific treatments) prior to starting study treatment or administered after the patient starts study treatment.
The investigator should instruct the patient to notify the study site about any new medications (including over-the-counter drugs and herbal/alternative medications) he/she takes after the start of study treatment. Patients must be instructed not to take any additional medications (including over-the-counter products and herbal/alternative medications) during the trial without prior consultation with the investigator.
The investigator may remind the patient to notify any change or any new medication in the personal booklet delivered at the randomisation.

7.7.2. Interactions and precautions : allowed and prohibited therapy

Patients receiving standard maintenance drugs should be advised of contraindications with food or nutritional supplements or drug herbal medications or regarding lifestyle, if any, according to the Summary of Product Characteristics recommendations.

Patients receiving one of the SAFIR02 investigational study drugs should be advised of contraindications with any other drug, if applicable, according to the Summary of Product Characteristics recommendations and/or Investigator Brochure. A summary for each study drug is outlined in the Table 17.

As a general rule, the use of drugs that can disrupt electrolyte levels should be avoided to the extent possible. Drugs that can disrupt electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids

The above list of potentially interacting drugs is not comprehensive.

Table 17: Interactions and precautions with investigational study drugs during the treatment phase

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
AZD2014 Vistusertib	Based on in vitro data, vistusertib may precipitate drug interactions due to inhibition of OATP1B1, OATP1B3, MATE1 and MATE2K. In addition, vistusertib is an inducer of CYP3A4 in vitro. Taking specific substrates of OATP1B1, OATP1B3, MATE1 and MATE2K is not allowed during the trial. In vitro, vistusertib is a substrate CYP3A4/5, for P-gp and BCRP. Coadministration with inhibitors/inducers of these enzymes and transporters may increase/decrease exposure to AZD2014. Strong or moderate inhibitors /inducers of CYP3A4/5, P-gp and BCRP are not allowed during the trial.	Co-administration of vistusertib that in some reports might be associated with Torsades de Pointes with drugs that could induce Torsades de Pointes (identified as of possible or conditional risk) should be avoided during the study. However, these drugs can be allowed, at the discretion of the investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks for QTc and electrolytes.	Regular anticoagulant therapy are allowed. Patients who begin warfarin or coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving vistusertib. Patients may continue to receive therapeutic bisphosphonates and erythropoietin preparations (Procrit, Epogen, Aranesp), if they were receiving them prior to beginning study treatment. For patients receiving high doses of allowable statins, eg. atorvastatin or simvastatin, dose reductions of the statin should be considered in line with manufacturers SmPC or prescribing information.	It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.
AZD4547	AZD4547 is a substrate of CYP3A4 and CYP2D6 therefore use of inhibitors/inducers of these isoforms should be excluded for the duration of study treatment. In addition, AZD4547 shows weak competitive inhibition of CYP3A4 and is also a time-dependent inhibitor of this isoform. This may lead to reduced metabolism (and increased exposure) of any co-administered drugs that are significantly cleared via this pathway.	No described risk	During AZD4547 treatment, patients should not be administered calcium-containing phosphate chelation agents, such as calcium acetate, for the management of hyperphosphataemia while receiving study treatment.	Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits. CYP1A1, an isoform highly inducible by cigarette smoking, is also capable of metabolism of AZD4547 and may lead to lower exposures in smokers.

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
	Concomitant use of medicines significantly metabolised by CYP3A4 will be contraindicated during the course of the study. Use of other agents less significantly metabolised may be permitted with caution if considered clinically indicated for the welfare of the patients, and patients should be closely monitored for possible drug interactions.			
AZD5363	In vivo experiments indicate that AZD5363 is an inhibitor of CYP3A4. AZD5363 is itself a substrate of CYP3A4. AZD5363 is also a moderate inhibitor of CYP2D6 in vitro. Coadministration of CYP3A4 inhibitors may increase exposure to AZD5363. In addition, coadministration of CYP3A4 inducers may decrease the exposure to AZD5363. AZD5363 is also a moderate inhibitor of CYP2D6 in vitro. This may increase the exposure of drugs metabolised via CYP2D6. Use of potent inhibitors or inducers of CYP3A4 should be avoided during the trial. All patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to potently modulate CYP3A4 enzyme activity during the trial. All patients should avoid concomitant use of drugs and herbal supplements known to be CYP3A4 or CYP2D6 substrates during the trial. If co-administration is necessary during the study for appropriate clinical care then additional monitoring for signs of toxicity related to increased exposure to the substrates may be required. Drugs that are significantly metabolised by	Co-administration of AZD5363 that in some reports might be associated with Torsades de Pointes with drugs that could induce Torsades de Pointes (identified as of possible or conditional risk) should be avoided during the study. However, these drugs can be allowed, at the discretion of the investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks for QTc and electrolytes.	Patients who begin warfarin or coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving AZD5363. For AZD5363 coadministration with statins (atorvastatin (ATV),cerivastatin (CRV), lovastatin (LOV), and simvastatin (SMV)), the potential for CYP-mediated drug-drug interactions is high. However, there is minimal metabolism of fluvastatin (FLV), pravastatin (PRV), or rosuvastatin (RSV) by CYP3A4 and thus plasma levels are minimally influenced by CYP3A4 inhibitors, conveying a relatively low potential for clinically significant drug-drug interactions with AZD5363 via this mechanism. When statins are required for a	Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
	CYP2B6, CYP2C9 or CYP2C19 and have a narrow therapeutic margin are permitted during the treatment phase but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co administration with AZD5363. Haloperidol and tramadol and other agents with narrow therapeutic windows that are known to depend on combined CYP3A4 and CYP2D6 metabolism should not be associated with AZD5363.		patient, the agents RSV, PRV and FLV should be preferred. It is recommended that, if used, doses of RSV be capped to 10 mg once daily, and PRV be capped to 40 mg once daily when combined with AZD5363, and for a 2 week period before and after AZD5363 treatment. No dose cap is required for FLV.	
AZD8931	The principal human P450 involved in metabolism appeared to be CYP 3A4, with a minor contribution from CYP 2D6 under the experimental conditions used. As little of the clearance in man appears to be mediated via the CYP2D6 route, any potential risk of drug-drug interactions with AZD8931 lies with co-administered inhibitors and inducers of CYP3A4. AZD8931 did not show a marked potential for clinically relevant inhibition or induction of any major CYP isoform. Although AZD8931 and its O-desmethyl metabolite were both shown, in vitro, to have the potential to inhibit BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 uptake transporter proteins, the risk of causing drug-drug interactions with substrates of these transporter proteins is considered to be low.	Co-administration of AZD8931 that in some in vitro reports might be associated with Torsades de Pointes with drugs that could induce Torsades de Pointes (identified as of possible or conditional risk) should be avoided during the study. However, these drugs can be allowed, at the discretion of the investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks for QTc and electrolytes.		It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
Selumetinib	Co-administration of selumetinib with potent CYP3A4 or 2C19 inhibitors may increase selumetinib exposure, whereas co-administration with potent CYP3A4 inducers may decrease exposure to selumetinib. Inhibitors/inducers of CYP1A2 could be impacted by selumetinib. It is therefore recommended that patients should avoid taking potent CYP2C19 inhibitors or potent CYP3A4 inhibitors/inducers, unless considered clinically indicated.	No described risk	Patients who begin warfarin or coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving selumetinib (contains vitamin E that may potentiate the anticoagulant activity of coumarins). As selumetinib capsules contain vitamin E, patients should not take vitamin E or multivitamin supplements which provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E. The maximum dose of vitamin E patients may receive from selumetinib is approximately 270 mg/day.	It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.
Vandetanib	A potent CYP3A4 inducer has been shown to reduce the exposure to vandetanib by 40% thus the co-administration of such inducers with vandetanib is not allowed. A potent CYP3A4 inhibitor has been shown have little effect on the exposure to vandetanib and therefore these can be co-administered with vandetanib during the trial if clinically indicated. In vitro data has shown vandetanib inhibits CYP2D6 and CYP2C8. Thus substrates of both CYP2D6 and CYP2C8 may be co-administered with vandetanib during the trial if clinically indicated.	The concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes with vandetanib at risk of QTc prolongation are not allowed within 2 weeks of randomization or during the study. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment. Concomitant use of medicinal products known to	Exposure to metformin or digoxin is increased when administered in combination with vandetanib. Patients receiving concomitant metformin or digoxin and vandetanib should be monitored as appropriate and may require a lower dose of metformin. Omeprazole may decrease vandetanib plasma concentrations, an other equivalent drug should be used.	It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
		also prolong the QTc interval and / or induce Torsades de pointes, should be avoided with vandetanib.	Caution should be used when administering Vandetanib to patients with brain metastases as intracranial haemorrhage has been reported.	treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.
Olaparib	Known strong CYP3A inhibitors or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg bd for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards. Moderate CYP3A inhibitors - reduce the dose of olaparib to 150mg bd for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards. After the washout of the inhibitor is complete, the olaparib dose can be re-escalated. Strong and moderate CYP3A inducers of CYP3A should not be taken with olaparib. If the use of any strong or moderate CYP3A	No described risk	Patients who begin warfarin or coumadin therapy should be advised to have their anticoagulation monitored more frequently when receiving olaparib In vitro, olaparib has been shown to be an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. Olaparib is predicted by PBPK modelling not to be a Pgp inhibitor in vivo. However, it cannot be excluded that olaparib may modulate the exposure to substrates of Pgp, OATP1B1 , OCT1, OCT2, OAT3, MATE1 and MATE2K). In particular, caution should be exercised if olaparib is administered in combination with any statin.	Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
	inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib. It is possible that co-administration of P-gp inhibitors (eg amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed. Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp. Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.			
Savolitinib	At the clinical exposures observed for savolitinib, a drug interaction with substrates of CYP2C8 and/or CYP3A4/5, or P-gp cannot be discounted. Consequently, the exposure of any medications whose exposure is dependent on CYP2C8, CYP3A4/5 or P-gp may be increased if co-dosed with savolitinib. Investigators are advised to use caution when prescribing drugs that are substrates of CYP3A4/5. Caution is advised if strong CYP2C8 substrates (those almost exclusively metabolised by CYP2C8) are used concomitantly and if drugs that are known to be affected by P-gp are to be used	No described risk	Granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, platelet-stimulating factors, or erythropoietin are specifically prohibited concomitant therapies.	It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
	concomitantly. Caution is also advised if strong CYP2C9 substrates (those almost exclusively metabolised by CYP2C9 and/or with a narrow therapeutic window such as warfarin) are co-administered. The frequency of INR tests should be increased if savolitinib and warfarin are used concomitantly.			requirement for dose reduction of study treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.
Vemurafenib	Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolised by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolised by CYP3A4, including oral contraceptives. Dose adjustments for medicinal products predominantly metabolised via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with Vemurafenib. Vemurafenib may increase the plasma exposure of medicinal products that are P-gp substrates. Caution should be exercised, dose reduction and/or additional drug level monitoring for P-gp substrate medicinal products with narrow therapeutic index (NTI) (e.g. digoxin, dabigatran etexilate, aliskiren) may be considered if these medicinal products are used concomitantly with Vemurafenib. Vemurafenib pharmacokinetics could be affected by medicines that inhibit or influence P-gp. Concomitant administration of potent	The concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes with Vemurafenib at risk of QTc prolongation are not allowed within 2 weeks of randomization or during the study. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment. Concomitant use of medicinal products known to also prolong the QTc interval and / or induce Torsades de pointes, should be avoided with Vemurafenib.	Vemurafenib has minor influence on the ability to drive and use machines. Patients should be made aware of the potential fatigue or eye problems that could be a reason for not driving. Exercise caution and consider additional INR (International Normalised Ratio) monitoring when Vemurafenib is used concomitantly with warfarin.	It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
	inducers of P-gp, glucuronidation, CYP3A4 should be avoided when possible. Alternative treatment with less inducing potential should be considered to maintain the efficacy of Vemurafenib. Certain medicines are broken down (metabolised) by enzymes such as CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.			
Cobimetinib	Concurrent use of strong CYP3A inhibitors during treatment with Cotellic should be avoided. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with Cotellic. If concomitant use with a strong or moderate CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety and dose modifications applied if clinically indicated. Cobimetinib can be co-administered with mild inhibitors of CYP3A without dose adjustment. Concomitant use of moderate and strong CYP3A inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort) should be avoided. Alternative agents with no or minimal CYP3A induction should be considered. Given that cobimetinib concentrations are likely to be significantly reduced when co-administered with moderate to strong CYP3A inducers, patient's efficacy may be compromised. Cobimetinib is a substrate of P-glycoprotein	No described risk	No described risk	It is strongly recommended that patients follow a program of sun protective measures during the treatment course for 3 months after discontinuing study treatment. The use of sun beds or tanning booths (including dye-based tanning booths) should be avoided during this time . Sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) should be used when exposed to sunlight during this period of time. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study treatment. Patients must be instructed to avoid grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits.

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
	(P-gp). Concomitant administration of P-gp inhibitors such as ciclosporin and verapamil may have the potential to increase plasma concentrations of cobimetinib.			
Durvalumab	No described interactions	No described risk	Live virus and bacterial vaccines (e.g yellow fever vaccine) should not be administered 30 days prior to or while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed or could occur. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses over 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers should be excluded during the study. Use of immunosuppressive	No described risk

Study drug	CYP, Pgp, BCRP	QT interval-prolonging drugs	Other	Lifestyle Interactions
			medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).	

7.7.3.Permitted medications and non-drug therapies

Subjects should receive full supportive care during the study, as clinically indicated and at the discretion of the investigator, including transfusion of blood and blood products, hematopoietic growth factors, treatment with antibiotics, antiemetics, antidiarrheals, analgesics, etc. Antiacids are allowed.

Concurrent treatment with appropriate hormone replacement therapy or bisphosphonate or stable low dose of corticosteroids are allowed (unless contra-indicated) provided that they were initiated before the last disease progression or were started at least 4 weeks prior to treatment with SAFIR02 study drugs.

Other medication that is considered necessary for the patient's safety and well-being may be given at the discretion of the investigators.

Prior to initiating a treatment, it is recommended to consult Table 17 for potential interactions and contraindications with investigational study drugs.

Palliative radiotherapy is allowed provided disease progression is not the indication. **Sponsor should be contacted** before initiating radiotherapy to discuss on a case basis the appropriate management of the study drug (interruption and resuming study treatment).
In case radiotherapy is administered to all evaluable lesions prior to achieving a confirmed PR or CR, the patient will become non-evaluable for primary endpoint of this trial. In case there are enough evaluable lesions outside the radiotherapy field, evaluation can proceed on those remaining lesions.

In the event elective surgery is necessary during study participation, **sponsor should be contacted** for appropriate management of study drug dosing.

7.7.4.Prohibited medications and non-drug therapies

No other chemotherapeutic agents or investigational drugs should be administered while patients are receiving study medication. Patients requiring anti-cancer therapies other than the study medication, with the exception of palliative radiotherapy (refer to section 7.7.3), must be discontinued from the study.

Patients must be instructed not to take any additional herbal medications during the trial without prior consultation with the investigator.

Live virus and bacterial vaccines (e.g yellow fever vaccine) should not be administered 30 days prior to or while the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed or could occur with some targeted therapies or conventional myelosuppressive chemotherapy (i.e pemetrexed) and with MEDI4736.

Prior to initiating a treatment, it is recommended to consult Table 17 for potential interactions and contraindications with investigational study drugs.

8. STUDY ASSESSMENTS AND PROCEDURES FOR THE SCREENING PHASE

8.1. Screening assessments

Patient flow-chart is described in Appendix 1a.

An informed consent form must be signed before the evaluations required for inclusion and any study specific procedure are performed.
A procedure or evaluation already performed within the standard of care and which is in accordance with the protocol requirements does not need to be repeated unless clinically justified.

8.1.1. Demographic data and disease history

- Date of birth, gender, height
- Histopathological diagnosis
- Known tumor characteristics: hormone receptor status (IHC for progesterone, estrogen and androgen receptors), HER2 status of the primary tumor or the metastasis (IHC and FISH/CISH/SISH) and BRCA1 and 2 constitutional mutation status.
- Familial history of cancer for patients who present a somatic mutation of BRCA1, BRCA2, ATM, PALB2, identified by the SAFIR02 NGS panel.
- Clinical characteristics: age at diagnosis, stage at diagnosis, date of diagnosis of the metastatic relapse, metastatic site(s) at inclusion, disease status at inclusion;
- Previous or current treatments: surgery, radiotherapy, adjuvant or neoadjuvant chemotherapies received, hormone therapy, treatments for metastatic disease.
- Relevant medical history other than the studied disease
- Check the current administration of prohibited medications for the randomized part of the study and start considering substituting them.

8.1.2. Clinical Examinations (≤ 14 days before inclusion request)

- Complete physical examination (major body systems)
- Vital signs (blood pressure, oxygen saturation, heart rate, temperature)
- ECOG performance status
- Signs and Symptoms
- Weight

8.1.3. Biological tests (≤ 14 days before inclusion request)

If a biopsy is planned for the screening phase, the following biological tests should be performed. Otherwise (i.e archived tumor or ctDNA used for screening), they are not requested.

- Haemogram: haemoglobin, differential count, platelets
- Biochemistry: sodium, potassium, calcium, magnesium, fasting plasma glucose, bicarbonate, chloride, urea, creatinine, ASAT, ALAT, ALP, total bilirubin, total protein, albumin, phosphorus.
- Coagulation profile: PT/INR, aPTT
- Pregnancy test for women of childbearing potential: β-HCG test to be performed within 14 days prior to the biopsy, or urine test to be performed within 72 hours. The results must be reviewed prior to undergoing the biopsy procedure

In addition, if the biopsy is performed at distance of the inclusion authorization (more than 5 days), biological tests should be perfomed again.

8.2. Patient registration procedure (before biopsy procedure)

After the patients have signed the informed consent form for the screening phase and all inclusion and exclusion criteria have been checked, eligible patients will be registered through the R&D Unicancer online e-CRF.

https://ecrf.icm.unicancer.fr/CSOnline/

An automatic reply, followed by an e-mail will confirm the success of the inclusion procedure and will deliver an inclusion number. The 5 digits number preceded by the letter B (for Breast) will identify the participating site on the first 2 digits followed by the position of the patient included (e.g B01003 for the third patient included in the site identified 01 in the SAFIR02 Breast study).
This number must be used as the sole patient identification (ID) number throughout the study especially for the identification of biological samples.

8.3. Samples for genomic analysis

Fresh tumor specimen, FFPE tumor specimen, FFPE cytoblock obtained with a fine-needle aspiration or blood plasma can be used to perform the genomic profile of the patient.
Tumor samples can be a metastasis or a primitive tumor specimen (only when locally advanced or stage IV at diagnosis).
Blood plasma can be used only if it has been collected on purpose for ctDNA extraction and if blood has been collected ideally before initiating chemotherapy.

However, the collection of tissue must be promoted in the perspective of further additional research objectives. Therefore, the following order of priority should be strictly applied when providing a sample at inclusion:

1/ an attempt should be made to provide fresh tumor samples
2/ if the cellular content of the fresh sample is <30% and /or the biopsy is not feasible (e.g. inaccessible location, only bone metastasis, or patient real safety concerns), an archived FFPE sample can be provided (collected less than 1 year ago) as well as fine-needle aspiration preserved in FFPE cytoblock (collected less than 1 year ago)
3/ as an ultimate solution, blood plasma can be used in situations where no tissue sample, fresh nor FFPE, is eligible (tumor cells<30% or insufficient sample size) and biopsy is an absolute contraindication or bone metastasis is the only site of biopsiable disease.

Any sample should be collected after the patient ID has been obtained by the center in order to assure that samples will be correctly identified. Inverting this sequence is not recommended as it may lead to a suboptimal procedure or to the misidentification of specimens (samples undergo more handling while they wait for getting the ID number, and the risk of error is increased).

If an archived frozen or FFPE sample is used, it must be first identified with the study patient ID number before being sent to the genomic platforms for DNA extraction and genomic analysis.

8.3.1. Biopsy procedure

The choice of the site of biopsy is left to the judgment of the research team, who will assess the feasibility of the procedure according to the accessibility and volume of the metastasis. The biopsy will be carried out in accordance with local recommendations.
If none of the frozen biopsy cores are suitable to characterize the anomalies of the tumor, a second biopsy may be suggested to the patient as long as the inclusion criteria are still met. The decision to perform a second biopsy is left to the investigator and his/her team, so is the choice of the sampled site which may be the same as or different from the initial biopsy.

In the perspective of translational studies, the samples must be core biopsies.

At least three core biopsies shall be collected:

- two biopsies to be frozen in nitrogen or fixed by the OCT method described in appendix 2. The first biopsy will be used for DNA extractions. The second biopsy will be stored as such at -80°C until the sponsor requests its transfer. It will be used for proteome studies or for complete genome sequencing.

- one biopsy will be fixed and embedded in paraffin according to the methods described in appendix 3. If the tumor presentation allows it, a second fixed biopsy would be desirable for the planned IHC studies.

If the metastasis volume is not sufficient to obtain three biopsy cores, priority will be given to the frozen sample for extracting nucleic acids, and then to the fixed and paraffin-embedded biopsy.

The informations regarding the choice of the biopsied site and detailed conditions of sampling will be collected in a specific form of the e-CRF.

Only frozen samples with at least 30% of tumor cells will be sent to the platforms for the genomic analysis.

8.3.2.FFPE sample

Archived FFPE samples identified for the genomic analysis should be thoroughly selected by the local pathologist. As for frozen samples, a 30% threshold will be applied.
The samples processing procedures for the pathologist are described in a document given apart from this protocol.

8.3.3.CtDNA plasma samples

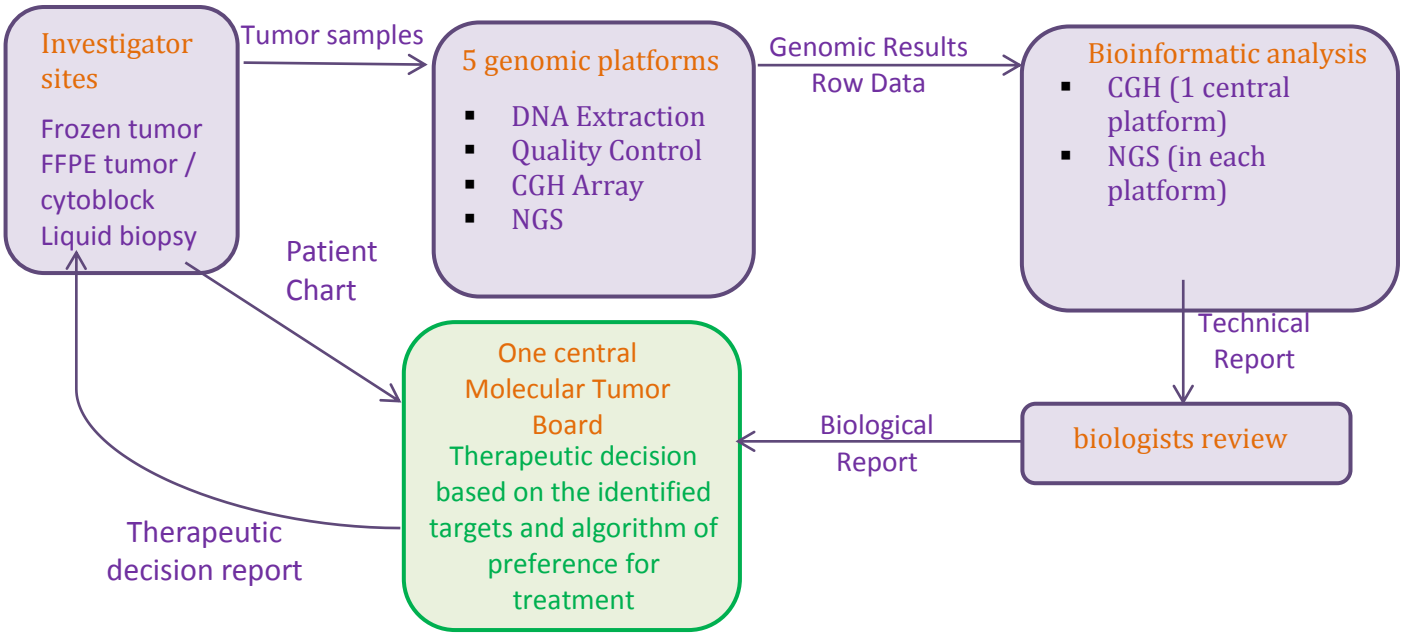
The plasma samples to be used for genomic analysis will be taken from the collection of plasma tubes collected at screening (refer to section 8.4). 2 *1.5 mL plasma tubes will be shipped to the platform.
Ideally samples should be collected before chemotherapy, otherwise ctDNA concentration may be modified by chemotherapy and the analysis may be not feasible. The time limit to collect the plasma for ctDNA is before initiating cycle 3 of chemotherapy.

8.4. Blood samples

FOR ALL THE CENTERS
For these patients who gave their approval, a 3x10 mL blood sample will be collected ideally before initiation of chemotherapy for ct DNA analysis, before cycle 3 at the latest.
The sampling and processing procedure are described in a document given apart from this study protocol.
⚠ whole blood transfusion within 120 days of the date of the ctDNA sample collection will exclude patient from the optional ctDNA and genetic evaluation.

8.5. High throughput molecular analysis

8.5.1. General organization for tumor samples



8.5.2. Quality control and DNA extractions

The frozen or FFPE samples will be first analysed by the local pathologist using conventional histology techniques to determine the percentage of cancerous cells.
If the sample contains 30% or more cancerous cells, it will be sent to the closest molecular analysis platform or to the one chosen by the centre.
The histopathological report will be collected in the CRF.
The report and the HES slide used for the % tumor cell determination will be sent along with the biopsy to the platform.

If the tumor sample or the FFPE cytoblock contains less than 30% tumor cells, and performing a new biopsy is not achievable for the patient, plasma samples will be sent to the platform. No specific control quality has to be performed by the site, except a visual control to check that the requested quantity of plasma is sent for analysis.

The samples processing procedures and extraction conditions for the platforms are described in a document given apart from this protocol.

8.5.3. DNA microarrays Arrays CGH

Arrays CGH will be performed either with Affymetrix CytoScan®–assays for fresh tumor DNA or Affymetrix OncoScan® assays for FFPE or ctDNA.
Hybridization scans and sequences will be sent to the central Gustave Roussy bioinformatics platform. BioIT will determine which genes exhibit high level amplifications or genomic losses.
Genomic plots will be generated and made available to the MTB together with raw results for the list of selected genes (listed in appendix 4).

8.5.4. Next Generation Sequencing

Next generation sequencing will be performed with Ion Torrent PGM, or Illumina MiSeq/MiniSeq, and AmpliSeq technology, using a panel of around 70 genes listed in appendix 4.
Each platform will generate a report displaying all the relevant mutation. This report will be validated by a biologist before making it available to the MTB.

8.6. Molecular Tumor Board (MTB)

A central MTB will be organised with the aim of discussing the genomic profiles and at providing a therapeutic decision for each patient. The MTB will consider the current clinical status of the patient, including general health, disease specifics, concomitant conditions, current and previous therapies, and genomic analysis. The MTB will collectively designate the more relevant abnormality to target with one of the targeted drugs of the panel (refer to Appendix 5).

The therapeutic decision will be supported by a predefined algorithm (see Appendix 6). As a general principle:
a. It will take into account, as the first priority, amplifications and mutation on the actionable gene of a drug. If two events coexist, patient will receive the most efficient drug according to available clinical data.
b. In the absence of a mutation or amplification on a gene that can be directly targeted, abnormalities on pathways will be taken into consideration.

The MTB will meet every other week by webconference. The MTB members will consist of oncologists experts from the French CLIP^2 network that are currently participating centers in the SAFIR02 trial, of genomic platforms representatives, of bioinformaticians and of bio-pathologists.
Investigators whose patients will be discussed during a meeting will be encouraged to attend the conference. Any other investigator or genomic-analysis-related personnel will be a welcome addition.

Any decision of the MTB will be notified to the patient's physician through a clinical report validated by the designated Chair of the MTB.

Every generated molecular profile will be reviewed by the MTB regardless of the patient's disease status (responding or progressing).

9. STUDY ASSESSMENTS AND PROCEDURES FOR THE RANDOMIZED PHASE : SUBSTUDY 1

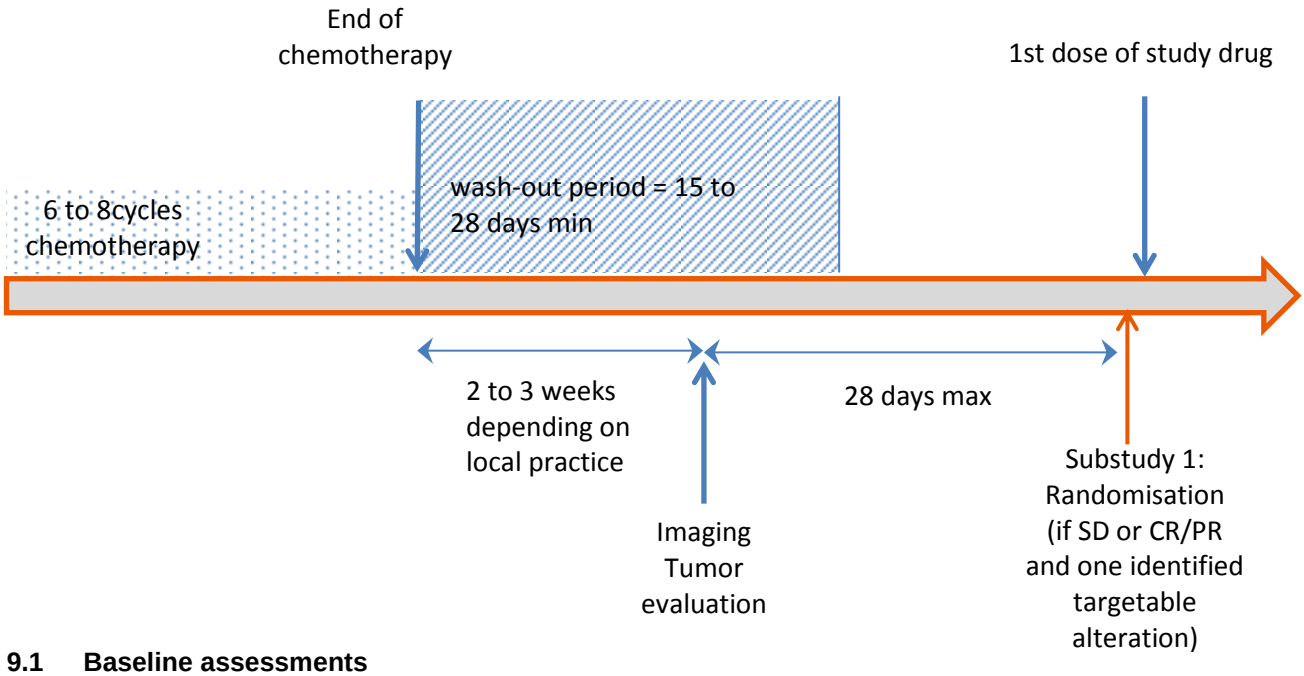
Patients can be considered as pre-eligible for the substudy 1 randomisation phase when both following mandatory conditions are met:

- stable or responding disease (investigator's judgment) is observed after 6 to 8 cycles of chemotherapy (or at least after 4 if treatment stopped for toxicity)
- one targetable alteration with the corresponding targeted study drug is identified by the Molecular Tumor Board.

Patients who cannot be randomized in the substudy 1 can be oriented to the immunotherapy substudy 2.

Then the patients will have to sign a second specific informed consent form for the randomization phase, depending on the substudy the patients are directed to, in order to initiate all the selection and baseline assessments. The mandatory post-chemotherapy wash-out period of 15 days for weekly (except monoclonal antibodies) or daily chemotherapies and of 28 days for the other chemotherapies regimen, will provide time to achieve all the required tests and examinations.

The randomization of eligible patients will be performed within a maximum of 28 days after tumour assessment.



9.1 Baseline assessments

Patient flow-chart is described in Appendix 1b. It provides the safety and efficacy assessments that must be performed **to every patient** at baseline.

An informed consent form must be signed before the evaluations required for randomization and any study specific procedure are performed.
A procedure or evaluation already performed within the standard of care and which is in accordance with the protocol requirements does not need to be repeated unless clinically justified.

9.1.1 Baseline conditions

- Check that all screening inclusion and exclusion criteria are still met
- Previous chemotherapy
    - record all compounds received, schedule, doses and number of cycles

- collect the residual toxicities before study treatment initiation.

- Check contraceptive methods:

  Females of child-bearing potential should use two forms of highly reliable methods of contraception. Acceptable contraceptive conditions, for patient or partner, while on treatment, beginning 2 weeks before the first dose of study product and for at least 4 months after the last dose of study drug include:

  - Established use of oral, injected or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system.
  - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
  - Male partner sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
  - True abstinence.
  - Hormonal contraception

  or

  Patients must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

  - Post-menopausal – defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
  - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.

  Male patients should use barrier contraception (ie, condoms).). It is not known whether the preclinical changes seen in the male animal reproductive organs, after treatment with AZD5363, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, if male patients wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

- Review of screening laboratory results: any result outside the normal range or inclusion range will be repeated (prior to the first dose) at the discretion of the investigator. Hypocalcemia, hypokalemia and hypomagnesemia should be corrected prior to any study drug administration;
- Concomitant treatments:
  - check the recent administration of inducers or inhibitors of CYP450 which are prohibited within 14 days prior to first dose,
  - check the administration of other forbidden therapy and consider substituting them, where possible
  - record all medication(s) received within 2 weeks (or before) prior to the first dose of the study treatment that may interact with one of the study drugs or may induce or potentiate some drugs related adverse events (refer to table 17) and note if the medication is continuing.
- Record relevant adverse events related to the biopsy procedure.

Summary of Product Characteristics recommendations will be followed for patients receiving non targeted maintenance drugs.

9.1.2 Tumor assessment (≤ 28 days)

Common to all patients

- Clinical disease assessment for palpable or visual lesions
- Mandatory CT scan or MRI of the chest, abdomen, and pelvis for baseline RECIST assessment. If performed, PET-scan cannot be used for RECIST assessment

  Note that : a mandatory recording on a CD is requested (refer to section 13.2)
- Other appropriate radiologic assessment left to the investigator's discretion (e.g bone scan or brain if known metastases or if clinically indicated)
- Documentation of tumor status at time of randomization (CR, PR, or SD)

9.1.3 Clinical Examinations (≤ 14 days)

Common to all patients

- Complete physical examination (major body systems)
- Weight
- Vital signs (blood pressure, oxygen saturation, heart rate, temperature)
- ECOG performance status
- Collection of toxicities / adverse events / signs and symptoms

9.1.4 Paraclinical examinations and biological tests (≤14 days otherwise specified)

Common to all patients

- Triplicate12-lead ECG to obtain the QTc baseline reference and T-wave morphology, and other measurements: PR interval, QT interval, RR interval and QRS complex (digital ECG are recommended to calculate the standard intervals automatically). The same machine and the same correction method for QT should be used for the same patient all along the study.
- LVEF (echocardiogram or MUGA). The same method should be used throughout the study
- Hematology (refer to Table 18)
- Biochemistry (refer to Table 18) (Electrolytes should be obtained ≤ 7 days. Hypocalcemia, hypokalemia and hypomagnesemia should be corrected prior to study drug administration)
- Coagulation profile (refer to Table 18)
- Urinalysis (refer to Table 18)
- Pregnancy test for women of childbearing potential: β-HCG test to be performed within 14 days prior to the first dose of study treatment, but preferably, as close to the first dose of study treatment as possible, or urine test to be performed within 72 hours. The results must be reviewed prior to initiating treatment.

Table 18 : Laboratory collection plan

Test Category	Test Name
Hematology	haemoglobin, differential count, platelets
Biochemistry	sodium, potassium, calcium, magnesium, phosphorus, bicarbonate, chloride, fasting plasma glucose urea, creatinine, ASAT, ALAT, ALP, total bilirubin, total protein, albumin.
Coagulation profile	PT/INR, aPTT
Urinalysis (dipstick)	glucose, blood, protein
All laboratory analysis will be performed locally. Fasting conditions require that patients must be fasting overnight for at least 8 hours prior to the blood draw.	

9.1.5 Additional drug specific assessments

The appendix 1b provides drug specific flowcharts that list the safety and efficacy assessments to be performed additionally at baseline to patients guided to a specific drug.

Vistusertib

- Thyroid function tests: TSH, T4, T3
- Fasting lipids profile : triglycerides, HDL, LDL, cholesterol
- Glycosylated haemoglobin (HbA1C)
- Cardiac markers : creatinine kinase, CK-MB, troponins I and T measurements
- Urinalysis : sodium, potassium, urea, creatinine

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- Fasting lipids profile : triglycerides, HDL, LDL, cholesterol
- Glycosylated haemoglobin (HbA1C)
- Insulin and insulin C-peptide

- Troponin I and T measurements

AZD4547

- Troponin I and T measurements
- Ophthalmic examination (refer to section 12.1.3.8 for detailed assessments) including OCT scan performed by an ophthalmologist or licensed practitioner in ≤ 28 days

AZD8931

Ophthalmic examination (refer to section 12.1.3.8. for detailed assessments) performed by an ophthalmologist or licensed practitioner in ≤ 28 days

Vandetanib

Thyroid function tests: TSH, T4, T3 only for patients receiving concomitant thyroid hormone replacement

Selumetinib

Ophthalmic examination (refer to section 12.1.3.8 for detailed assessments) performed by an ophthalmologist or licensed practitioner in ≤ 28 days

Savolitinib

Thyroid function tests: TSH, T4, T3

Vemurafenib + cobimetinib

- History of or ongoing retinal disease
- A complete dermatological history of prior medications and cuSCC risk factors (i.e radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions and photochemotherapy for psoriasis) must be collected;
- Dermatology evaluation by a dermatologist for cuSCC, basal cell carcinoma (BCC), actinic keratosis, keratoacanthoma (≤ 28 days). Anal and Head and Neck examination (as part of the evaluation for non-cutaneous SCC) performed by the dermatologist will consist of at least a visual inspection of oral mucosa and lymph node palpation;
- Gynecologic examination (≤ 6 months) is recommended;
- Chest CT scan prior to treatment as part of the evaluation of non-cuSCC (possibility of using the tumor assessment CT scan).

9.2 Patient randomization procedure

When all the criteria have been checked and are met, and after the mandatory period of 15 days (for daily or weekly chemotherapies) or 28 days (for 21-day and 28-day cycle chemotherapies and all monoclonal antibodies) has elapsed, the investigator will proceed with the randomization through the R&D Unicancer online e-CRF.

https://ecrf.icm.unicancer.fr/CSOnline/

An automatic reply, followed by an e-mail will confirm the success of the randomization procedure. The randomization program will allocate the following treatments with a 2:1 ratio in favor of Arm A:

- Arm A1 / targeted arm: targeted maintenance from a list of targeteddrugs, guided by the genomic analysis,

or

- Arm B1 / standard arm: standard maintenance as per guidelines.

9.3 Delivery of investigational product to the patient

- Study drugs will be dispensed for 1 cycle. Patients should be requested to bring back all used or unused bottles of treatment every cycle;
- Study staff will carefully instruct patients on how to take each study drug (refer to 7.6.1.1 and 7.6.1.2). The investigator may remind the patient how to manage concomitant medications (refer to section 7.7) and to notify any change or any new medication in the personal booklet delivered at the randomisation visit.

9.4 Follow-up assessments during treatment

The frequency of all the hereafter examinations and assessments performed during the treatment period are outlined in Appendix 1b through :

- a study flowchart that lists the safety and efficacy assessments as well as the visit schedule common to all the patients randomized in arm A1.

- several drug specific flowcharts that list the safety and efficacy assessments to be performed additionally to patients guided to a specific drug.

The following assessments are to be performed every 3 weeks (21 days except for vemurafenib+cobimetinib every 28 days) otherwise indicated in appendix 1b flowcharts, and as close to this interval as possible. Examinations, and laboratory assessments may be performed more frequently, if clinically indicated.
All laboratory tests with values that become significantly abnormal while the patient is participating in the study or within 30 days after the last dose of study therapy should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

A general +/- 2 days window is allowed for assessments or visits.

9.4.1 Clinical and paraclinical examination and biological tests

9.4.1.1 Common to all patients, whatever the treatment arm

- Complete physical examination (major body systems)
- Weight
- Vital signs (blood pressure, oxygen saturation, heart rate, temperature)
- ECOG performance status
- Toxicities / Adverse events
- Concomitant treatments (added and/ or changed)

9.4.1.2 Common to all patients in arm A1

- Hematology (see Table 18 for details)
- Biochemistry (see Table 18 for details)
- Coagulation profile (see Table 18 for details)
- Urinalysis (see Table 18 for details)
- Triplicate12-lead ECG

9.4.1.3 Drug specific

<u>Vistusertib</u>

- Heart rate (additional examinations)

- Blood pressure (additional examinations)
- Hematology (see Table 18 for details) (additional examinations)
- Biochemistry (Na, K, Ca, Mg, P, HCO3-, Cl, serum glucose and insulin, urea, creatinine)
- Coagulation test (see Table 18 for details)
- Urinalysis: Na, K, Urea, creatinine
- Triplicate12-lead ECG measurements and T-wave surveillance

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- Heart rate (additional examinations)
- Blood pressure (additional examinations)
- Fasting lipids profile : triglycerides, HDL, LDL, cholesterol
- Glycosylated haemoglobin (HbA1C)
- Insulin and insulin C-peptide
- Troponins I and T measurements
- Thyroid function tests: TSH, T4, T3
- Electrolytes (Na, K, Ca, Mg, P, HCO3-, Cl)
- FSH, oestrogen (females only), testosterone (males only)
- Urinalysis dipstick : proteinuria and glucose
- Random blood glucose (non-fasting)
- triplicate 12-lead ECG measurements
- LVEF (echocardiogram or MUGA)

AZD4547

- Troponins I and T measurements
- Calcium x phosphate product
- Ophthalmic exam
- OCT scan
- LVEF (echocardiogram or MUGA)

AZD8931

- Monitoring for pulmonary symptoms indicative of pneumonitis
- Ophthalmic exam only if an AE of visual disturbance occurs
- Triplicate 12-lead ECG measurements
- LVEF (echocardiogram or MUGA)

Vandetanib

- Monitoring for pulmonary symptoms indicative of pneumonitis
- Triplicate 12-lead ECG measurements

Selumetinib

- Monitoring for pulmonary symptoms indicative of pneumonitis
- Monitoring of muscle weakness
- Calcium x phosphate product
- Creatinine kinase
- Ophthalmic exam **only** if an AE of visual disturbance occurs.

Olaparib

- Hematology : reticulocytes, reticulocyte index and peripheral blood smear

Savolitinib

- Thyroid function tests: TSH, T4, T3
- LVEF (echocardiogram or MUGA)

- Creatine kinase only if fatigue occurs
- Urine dipstick and/or microscopy at regular intervals and in case of renal disorders

Vemurafenib + cobimetinib

- Assessment of symptoms of new or worsening visual disturbances or pulmonary disorders.
- Ophthalmic exam is recommended if an AE of visual disturbance occurs.
- Additional clinical examination at each visit performed by the investigator including inspection of the skin, anal margin and Head and Neck examination (as part of the evaluation for cutaneous and non-cutaneous SCC) consisting of at least a visual inspection of oral mucosa and lymph node palpation.
- Dermatology evaluation by a dermatologist 28 days (+/- 8 days) after starting vemurafenib + cobimetinib and every 12 weeks thereafter until drug discontinuation, for cuSCC, basal cell carcinoma (BCC), actinic keratosis, keratoacanthoma and second primary melanomas. Anal and Head and Neck examination (as part of the evaluation for non-cutaneous SCC) performed by the dermatologist will consist of at least a visual inspection of oral mucosa and lymph node palpation. In patients who develop cuSCC, dermatology examinations should occur monthly during and up to six months after treatment for cuSCC.
- Chest CT scan every 6 months during treatment as part of the evaluation of non-cuSCC (possibility of using the tumor assessment CT scan).
- Gynecologic examination is recommended when considered clinically indicated.
- LVEF should be evaluated the first month of treatment and at least every 3 months or as clinically indicated until treatment discontinuation. All patients restarting treatment with a dose reduction of cobimetinib after the management of a LVEF decrease should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.

9.4.1.4 Non targeted maintenance drugs for B1 arm

Summary of Product Characteristics recommendations and local standard practice will be followed for paraclinical examinations and biological tests.

9.4.2 Tumor assessment (every 6 weeks) (+/- 7 days) for efficacy

The following tumor evaluations shall be performed on target and non-target lesions.

- Clinical disease assessment for palpable or visual lesions
- CT scan or MRI of the chest, abdomen, and pelvis for RECIST assessment[≠]. If performed, PET-scan cannot be used for RECIST assessment
  Note that : a mandatory recording on a CD is requested (refer to section 13.2)
- Other appropriate radiologic assessment* left to the investigator's discretion (e.g bone scan or brain if known metastases or if clinically indicated).
- The same physician will evaluate the patient's tumor response/disease status at the end of each 6-week interval, when possible.
- Any new lesion(s) must be fully recorded in the CRF. If the lesion(s) noted at screening were not evaluated at the end of the 6-week interval, this will be noted as 'not done' (ND) in the CRF.
- Upon physical/ radiographic exam, if new ascites, pleural, or pericardial effusions are found in accessible regions and are cytologically evaluated, then the results should be recorded as malignant, non-malignant, or inconclusive in the patient's CRF. Any procedure to remove fluid from ascites, pleural, or pericardial effusions should be recorded in the source documents.

[≠]Radiographic disease assessments should be obtained every 6 weeks (+/- 7 days) or sooner, if clinically indicated. They should be repeated 4 weeks after assessment of a PR or CR as per RECIST guidelines.
*Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.

After 6 months from baseline, radiographic disease assessments will be obtained every 9 weeks until progression.

Upon disease progression, subsequent therapies will be given to the patient at the discretion of the investigator. Genomic profiles and MTB decision can be used by the physician's for the therapeutic decision. **However, a cross-over from the chemotherapy arm (arm B) to the investigational targeted therapy (arm A) is not allowed.**

9.4.3 Samples for ancillary translational studies

FOR ALL THE CENTERS.
A 3x10mL blood sample will be collected from all the randomized patients:
1/ immediately after the randomization procedure, and before the study drug initiation,
2 / and at the first disease assessment,

The sampling and processing procedure are described in a document given apart from this study protocol.

⚠ whole blood transfusion within 120 days of the date of the ctDNA sample collection will exclude patient from the optional ctDNA and genetic evaluation.

9.5 Assessments at therapy withdrawal

The protocol therapy can be administered as long as the patient benefits from treatment according to the physician judgement. The protocole therapy can be stopped for toxicity reasons, after progression, or after patient's or investigator's decision.

The following assessments will be performed if possible within the week after withdrawal for any reason and before initiating a new anti neoplastic treatment.

All patients with an ongoing toxicity at the time of the last dose of the study drug should have further appropriate assessments until toxicity has resolved.

The hereafter end-of treatment examinations and assessments are outlined in Appendix 1b through :
-a study flowchart that lists the safety and efficacy assessments to be performed to all the patients randomized in arm A1.
- several drug specific flowcharts that list the safety and efficacy assessments to be performed additionally to patients guided to a specific drug.

9.5.1 Clinical and paraclinical examination and biological tests

9.5.1.1 Common to all patients, whatever the treatment arm

- Complete physical examination (monitoring for pulmonary symptoms indicative of pneumonitis in patients treated with drugs at risk of ILD)
- Weight
- Vital signs (blood pressure, oxygen saturation, heart rate, temperature)
- ECOG performance status
- Toxicities / Adverse events
- Concomitant treatments (added and/ or changed)

9.5.1.2 Common to all patients in arm A1

- Triplicate12-lead ECG
- Hematology (see Table 18 for details)
- Biochemistry (see Table 18 for details)
- Coagulation profile (see Table 18 for details)
- Urinalysis (see Table 18 for details)

9.5.1.3 Drug specific

Vistusertib
- Monitoring for pulmonary symptoms indicative of pneumonitis
- Urinalysis : sodium, potassium, urea, creatinine
- Cardiac markers : only if clinically indicated

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- Fasting lipids profile : triglycerides, HDL, LDL, cholesterol
- Glycosylated haemoglobin (HbA1C)
- Insulin and insulin C-peptide
- Troponins I and T measurements
- Thyroid function tests: TSH, T4, T3
- FSH, oestrogen (females only), testosterone (males only)
- LVEF (echocardiogram or MUGA) only if clinically indicated

AZD4547
- Troponins measurement
- Calcium x phosphate product
- LVEF (echocardiogram or MUGA)

AZD8931
- LVEF (echocardiogram or MUGA). The same method as baseline should be used.

Selumetinib
- Monitoring for pulmonary symptoms indicative of pneumonitis
- Monitoring of muscle weakness
- Calcium x phosphate product

Vandetanib
- Monitoring for pulmonary symptoms indicative of pneumonitis

Olaparib
- Hematology : reticulocytes, reticulocyte index and peripheral blood smear

Savolitinib
- Creatine kinase only if fatigue occurs
- Thyroid function tests: TSH, T4, T3
- Microscopy of the urine at regular intervals in complement of urinalysis if clinically indicated
- LVEF (echocardiogram or MUGA)

Vemurafenib + cobimetinib

- Assessment of symptoms of new or worsening visual disturbances or pulmonary disorders.
- Ophthalmic exam is recommended if an AE of visual disturbance occurs.
- Additional clinical examination at each visit performed by the investigator including inspection of the skin, anal margin and Head and Neck examination (as part of the evaluation for cutaneous and non-cutaneous SCC) consisting of at least a visual inspection of oral mucosa and lymph node palpation.
- Dermatology evaluation by a dermatologist if not done within the last 12 weeks, for cuSCC, basal cell carcinoma (BCC), actinic keratosis, keratoacanthoma and second primary melanomas. Anal and Head and Neck examination (as part of the evaluation for non-cutaneous SCC) performed by the dermatologist will consist of at least a visual inspection of oral mucosa and lymph node palpation. In patients who develop cuSCC, dermatology examinations should occur monthly during and up to six months after treatment for cuSCC.
- Chest CT scan at 6 months after treatment discontinuation as part of the evaluation of non-cuSCC (possibility of using the tumor assessment CT scan).
- Gynecologic examination is recommended at the end of treatment.
- LVEF (echocardiogram or MUGA)

9.5.1.4 Non targeted maintenance drugs

Summary of Product Characteristics recommendations and local standard practice will be followed.

9.5.2 Tumor assessment

Tumor evaluation has to be performed if withdrawal was not related to disease progression. Otherwise, radiological assessments should not be repeated if they were obtained less than 6 weeks from withdrawal of therapy.

The following tumor evaluations shall be performed on target and non-target lesions.

- Clinical disease assessment for palpable or visual lesions
- CT scan or MRI of the chest, abdomen, and pelvis for RECIST assessment. If performed, PET-scan cannot be used for RECIST assessment
  Note that : a mandatory recording on a CD is requested (refer to section 13.2)
- Other appropriate radiologic assessment left to the investigator's discretion (e.g bone scan or brain if known metastases or if clinically indicated).

Upon disease progression subsequent therapies will be given to the patient at the discretion of the investigator. Genomic profiles and MTB decision can be used by the physician's for the therapeutic decision. **However, a cross-over from the chemotherapy arm (arm B) to the investigational targeted therapy (arm A) is not allowed.**

9.5.3 Drug compliance at every cycle

- return of all used / unused investigational product;
- assessment of study drug compliance / accountability;

9.5.4 Samples for ancillary translational studies

FOR ALL THE CENTERS

Immediately at disease progression, a 3x10mL blood sample will be collected from all randomized patients. The sampling and processing procedure are described in a document given apart from this study protocol.

 whole blood transfusion within 120 days of the date of the ctDNA sample collection will exclude patient from the optional ctDNA and genetic evaluation.

9.6 Post-treatment follow-up

9.6.1 For randomized patients

The duration of the post-treatment follow-up phase has been set up to at least 24 months.
Post- treatment follow-up schedule should be applied to the patients that were withdrawn from the randomized part of the study because they :

- experienced a disease progression
- developed an intolerable toxicity
- have received the complete doses of a standard chemotherapy regimen
- refused to continue on the study, or retrieved their consent
- were withdrawn from the study upon the investigator decision (e.g pregnancy, poor compliance, etc.)
- were withdrawn from the study upon the sponsor decision

For the patients who were withdrawn from the study for other reasons than disease progression, tumor assessments as per RECIST criteria should be continued and documented every 6 weeks during six months from baseline and then every 9 weeks until disease progression or initiation of an antineoplastic treatment.

One month and two months after end of treatment and on a quarterly basis thereafter:

- Disease and survival status: informations may be collected during visits or telephone calls.
- Clinical examination and vital signs
- Collection of persistent or long term occurring toxicities
- New antineoplastic therapies and concomitant treatments

On going toxicities or adverse event have to be monitored until resolution or returned to baseline level.
Adverse events must still be collected in the 30 days after the last investigational drug intake.
Any late Serious Adverse Drug Reaction (SAE related to the study drug), occurring at any time after the 30-day period must be reported to the R&D UNICANCER Safety Office.

Drug specific : vemurafenib + cobimetinib

- at each visit for a maximum of 6 months after last study treatment, clinical examination by the treating physician including skin, anal and Head and Neck examination (as part of the evaluation for cutaneous and non-cutaneous SCC) consisting of at least a visual inspection of oral mucosa and lymph node palpation;
- Patients should be monitored by a dermatologist for the occurrence of cutaneous and non- cutaneous neoplasms at months 3 and 6 after last study treatment.

9.6.2 For non-randomized patients

Non randomized patients are those that are not eligible for randomization in any substudy because they:

- experienced disease progression at any time during chemotherapy or before randomization or didn't achieve at least 4 full cycles of chemotherapy because of toxicity (except when patient is currently under the first line treatment and is progressing or discontinuing treatment because of toxicity reasons during the first 4 cycles, a second line treatment can be initiated before randomisation)

- present at least one exclusion criteria or didn't achieve all the inclusion criteria in both of the substudies
- receive a decision from the Molecular Tumor Board contraindicating the randomization in any substudy

Few follow-up information will be collected for these patients during 24 months after the date of inclusion in the screening phase:

- treatments received and responses to the treatments
- disease and survival status at 24 months

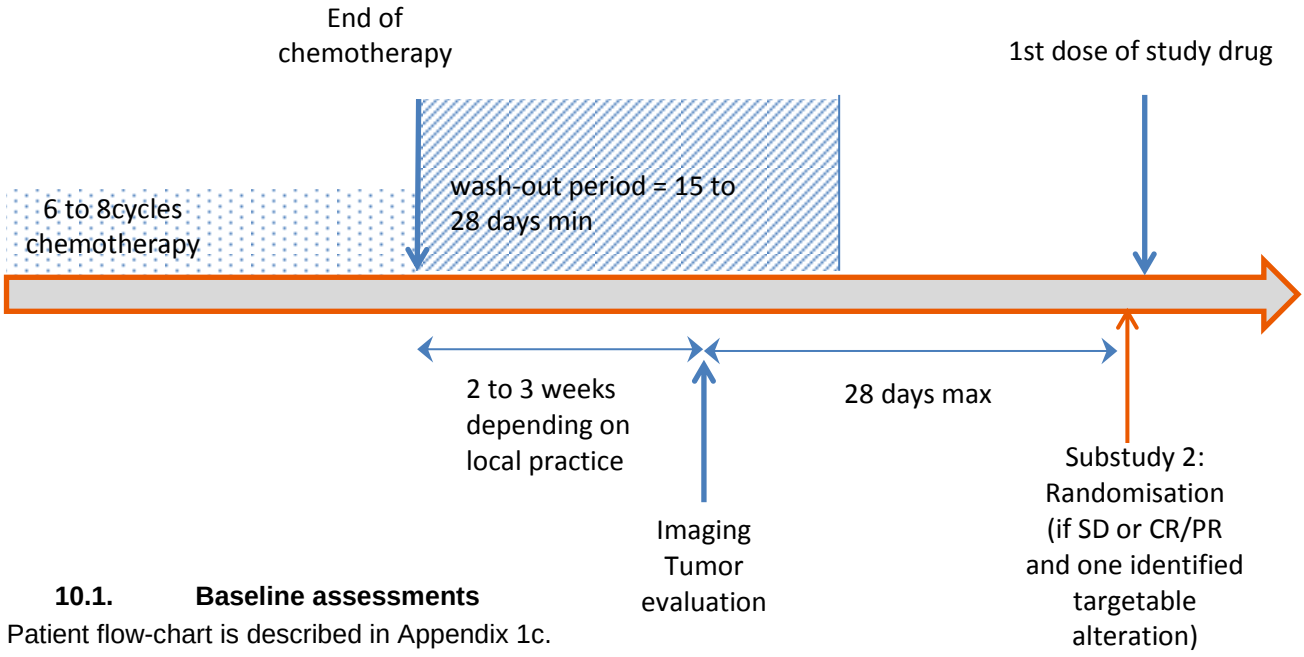
10. STUDY ASSESSMENTS AND PROCEDURES FOR THE RANDOMIZED PHASE :SUBSTUDY 2

Patients can be considered as pre-eligible for the substudy 2 randomisation phase when both following conditions are met :

- stable or responding disease (investigator's judgment) is observed after 6 to 8 cycles of chemotherapy (or at least after 4 if treatment stopped for toxicity)
- not eligible to randomisation in the substudy 1

Then the patients will have to sign a second specific informed consent form for the randomization phase, depending on the substudy the patients are directed to, in order to initiate all the selection and baseline assessments. The mandatory post-chemotherapy wash-out period of 15 days for weekly (except monoclonal antibodies) or daily chemotherapies and of 28 days for the other chemotherapies regimen, will provide time to achieve all the required tests and examinations.

The randomization of eligible patients will be performed within a maximum of 28 days after tumour assessment.



10.1. Baseline assessments

Patient flow-chart is described in Appendix 1c.

An informed consent form must be signed before the evaluations required for randomization and any study specific procedure are performed.
A procedure or evaluation already performed within the standard of care and which is in accordance with the protocol requirements does not need to be repeated unless clinically justified.

10.1.1. Baseline conditions

- Check that all screening inclusion and exclusion criteria are still met
- Previous chemotherapy
  - record all compounds received, schedule, doses and number of cycles
  - collect the residual toxicities before study treatment initiation.
- Check contraceptive methods:

  Females of child-bearing potential should use two forms of highly reliable methods of contraception. Acceptable contraceptive conditions, for patient or partner, while on treatment, beginning 2 weeks

before the first dose of study product and for at least 4 months after the last dose of study drug include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- Male partner sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence.
- Hormonal contraception

or

Patients must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal – defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.

Male patients should use barrier contraception (ie, condoms).

- Review of screening laboratory results: any result outside the normal range or inclusion range will be repeated (prior to the first dose) at the discretion of the investigator.
- Concomitant treatments:
  - check the administration of forbidden therapies and consider substituting them, where possible
  - record all medication(s) received within 2 weeks (or before) prior to the first dose of MEDI4736 that may interact and note if the medication is continuing.
- Record relevant adverse events related to the biopsy procedure.

10.1.2. Tumor assessment (≤ 28 days)

- Clinical disease assessment for palpable or visual lesions
- Mandatory CT scan or MRI of the chest, abdomen, and pelvis for baseline RECIST assessment. If performed, PET-scan cannot be used for RECIST assessment
  Note that : a mandatory recording on a CD is requested (refer to section 13.2)
- Other appropriate radiologic assessment left to the investigator's discretion (e.g bone scan or brain if known metastases or if clinically indicated)
- Documentation of tumor status at time of randomization (CR, PR, or SD)

10.1.3. Clinical Examinations (≤ 14 days)

- Complete physical examination (major body systems)
- Weight
- Vital signs (blood pressure, oxygen saturation, heart rate, temperature)
- ECOG performance status
- Collection of toxicities / adverse events / signs and symptoms

10.1.4. Paraclinical examinations and biological tests (≤14 days otherwise specified)

- Triplicate12-lead ECG to obtain the QTc baseline reference and T-wave morphology, and other measurements: PR interval, QT interval, RR interval and QRS complex (digital ECG are recommended to calculate the standard intervals automatically). The same machine and the same correction method for QT should be used for the same patient all along the study.
- Hematology: haemoglobin, differential count, platelets
- Liver enzyme panel : ASAT, ALAT, ALP, GGT, total bilirubin. **Note that** : if total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
- Biochemistry: sodium, potassium, calcium, magnesium, glucose, bicarbonate, chloride, urea, creatinine, total protein, albumin, amylase, lipase, lactate dehydrogenase, uric acid.
- Coagulation profile: PT/INR, aPTT
- Thyroid function tests: TSH, fT4, fT3
- Urinalysis : bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance
- Pregnancy test for women of childbearing potential: β-HCG test to be performed within 14 days prior to the first dose of study treatment, but preferably, as close to the first dose of study treatment as possible, or urine test to be performed within 72 hours. The results must be reviewed prior to initiating treatment.
- Hepatitis B surface antigen, hepatitis C antibody, HIV antibody

10.2. Patient randomization procedure

When all the criteria have been checked and are met, and after the mandatory period of 15 days (for daily or weekly chemotherapies) or 28 days (for 21-day and 28-day cycle chemotherapies and all monoclonal antibodies) has elapsed, the investigator will proceed with the randomization through the R&D Unicancer online e-CRF.

https://ecrf.icm.unicancer.fr/CSOnline/

An automatic reply, followed by an e-mail will confirm the success of the randomization procedure. The randomization program will allocate the following treatments with a 2:1 ratio in favor of Arm A:

- Arm A2 / immunotherapy arm: durvalumab

or

- Arm B2 / chemotherapy arm: chemotherapy continued as a maintenance chemotherapy (or no antineoplastic treatment in case of toxicity)

10.3. Administration and monitoring of durvalumab to the patient

- Durvalumab will be administered at hospital at Day 1 every 2 weeks;
- Durvalumab preparation will be administered as an IV infusion over approximately 60 minutes (+/- 5 minutes). Refer to Appendix 13 for dose calculation, preparation and administration description.
- Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the schedule of assessment during treatment (see Section 10.4)
- In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. Refer to

  Table 15 : Durvalumab management guidelines and dose modifications for management guidelines.
- As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study

personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary. Refer to Table 15 for management guidelines.

10.4. Follow-up assessments during treatment

10.4.1. Assessments for safety

The following assessments are to be performed as close as possible to this indicated intervals. Procedures, examinations, and laboratory assessments may be performed more frequently, if clinically indicated.

The frequency of all the following assessments and procedures are outlined in Appendix 1c.

All laboratory tests with values that become significantly abnormal while the patient is participating in the study or within 30 days after the last dose of study therapy should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Common to all patients whatever the treatment arm (every 4 weeks for durvalumab or every 3 to 4 weeks depending on the standard chemotherapy regimen) (+/- 2 days)

- Complete physical examination (major body systems)
- Weight
- Vital signs (blood pressure, oxygen saturation, heart rate, temperature)
- ECOG performance status
- Collection of toxicities / adverse events / signs and symptoms
- Concomitant treatments (added and/ or changed)

For patients treated with durvalumab

- Toxicities / Adverse events
- Concomitant treatments (added and/ or changed)
- Subjects will have their blood pressure and pulse measured before, during and after each infusion at the following times (based on a 60-minute infusion):
    - At the beginning of the infusion (at 0 minutes)
    - At 30 minutes during the infusion (±5 minutes)
    - At the end of the infusion (at 60 minutes ±5 minutes)
    - In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

  If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.
- Liver function tests : ASAT, ALAT, ALP, GGT, total bilirubin. **Note that** : if total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
- Haemogram: haemoglobin, differential count, platelets
- Biochemistry: sodium, potassium, calcium, magnesium, glucose, bicarbonate, chloride, urea, creatinine, total protein, albumin, amylase, lipase, lactate dehydrogenase, uric acid.
- Urinalysis : bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance
- Thyroid function tests: TSH, fT4, fT3
- Triplicate12-lead ECGs will be recorded within an hour prior to start of durvalumab infusion and at least one time point 0 to 3 hours after the infusion, for T-wave surveillance and for intervals measurements : QTc, PR, QT, RR, QRS complex (digital ECG are recommended to calculate the standard intervals automatically). The same machine and the same correction method for QT should be used for the same patient all along the study.

If the QTc is prolonged and >480ms (grade 2), 2 consecutive measurements must be collected approximately 10 minutes apart from the first abnormal measurement. Refer to section 9.1.4. for guidelines.

<u>For patients treated with non targeted maintenance drugs</u>

- Summary of Product Characteristics recommendations and local standard practice will be followed.

10.4.2. Tumor assessment (every 6 weeks) (+/- 7 days) for efficacy

 Immune-related response patterns are characterized in some patients by initial increase in size of tumor lesions, prior to a subsequent decreased tumor burden.
In order to avoid either misclassification as disease progression according to RECIST criteria or prematurely interruption of treatment**, the following guidelines must be observed during the first 2 disease assessments (at 6 and 12 weeks).**
In the event that the patient meets RECIST criteria for disease progression, the investigator should also consider the signs of clinical deterioration in order to correctly manage the situation.

- If the patient presents with signs and symptoms that could be related to disease progression : the patient is to be considered as having progressive disease and is to be withdrawn from treatment

- If the patient presents no clinical signs or symptoms that could be related to disease progression : treatment may be continued and a new clinical and radiological assessment should be performed 4 weeks later. If at this second assessment the disease is evaluated as stable or responding according to RECIST criteria, the patient will remain on study and treatment will be continued. If the progression is confirmed however, the treatment will be discontinued and the appropriate end of treatment evaluations performed.

The following tumor evaluations shall be performed on target and non-target lesions.

- Clinical disease assessment for palpable or visual lesions
- CT scan or MRI of the chest, abdomen, and pelvis for RECIST assessment[≠]. If performed, PET-scan cannot be used for RECIST assessment
  Note that : a mandatory recording on a CD is requested (refer to section 13.1.2)
- Other appropriate radiologic assessment* left to the investigator's discretion (e.g bone scan or brain if known metastases or if clinically indicated).
- The same physician will evaluate the patient's tumor response/disease status at the end of each 6-week interval, when possible.
- Any new lesion(s) must be fully recorded in the CRF. If the lesion(s) noted at screening were not evaluated at the end of the 6-week interval, this will be noted as 'not done' (ND) in the CRF.
- Upon physical/ radiographic exam, if new ascites, pleural, or pericardial effusions are found in accessible regions and are cytologically evaluated, then the results should be recorded as malignant, non-malignant, or inconclusive in the patient's CRF. Any procedure to remove fluid from ascites, pleural, or pericardial effusions should be recorded in the source documents.

[≠]Radiographic disease assessments should be obtained every 6 weeks (+/- 7 days) or sooner, if clinically indicated. They should be repeated 4 weeks after assessment of a PR or CR as per RECIST guidelines.
*Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.

After 6 months from baseline, radiographic disease assessments will be obtained every 9 weeks until progression.

Upon disease progression subsequent therapies will be given to the patient at the discretion of the investigator. Genomic profiles and MTB decision can be used by the physician's for the therapeutic decision. **However, a cross-over from the chemotherapy arm (arm B) to the investigational targeted therapy (arm A) is not allowed.**

10.4.3. Samples for ancillary translational studies

FOR ALL THE CENTERS
A 3x10mL blood sample will be collected from all the randomized patients:
1/ immediately after the randomization procedure, and before the study drug initiation,
2 / and at the first disease assessment,

The sampling and processing procedure are described in a document given apart from this study protocol.

 whole blood transfusion within 120 days of the date of the ctDNA sample collection will exclude patient from the optional ctDNA and genetic evaluation.

10.5. Assessments at therapy withdrawal

The protocol therapy can be administered as long as the patient benefits from treatment according to the physician judgement. The protocole therapy can be stopped for toxicity reasons, after progression, or after patient's or investigator's decision.

Upon disease progression subsequent therapies will be given to the patient at the discretion of the investigator. Genomic profiles and MTB decision can be used by the physician's for the therapeutic decision. **However, a cross-over from the chemotherapy arm (arm B) to the investigational targeted therapy (arm A) is not allowed.**

10.5.1. Clinical, tumor assessment and biological examinations

Assessments at therapy withdrawal will be performed about 30 days post-treatment and are outlined in section 10.6.

10.5.2. Samples for ancillary translational studies

FOR ALL THE CENTERS

Immediately at disease progression, a 3x10mL blood sample will be collected from all randomized patients. The sampling and processing procedure are described in a document given apart from this study protocol.

 whole blood transfusion within 120 days of the date of the ctDNA sample collection will exclude patient from the optional ctDNA and genetic evaluation.

10.6. Post-treatment follow-up

10.6.1. For randomized patients

The duration of the post-treatment follow-up phase has been set up to at least 24 months.
Post- treatment follow-up schedule should be applied to the patients that were withdrawn from the randomized part of the study because they :

- experienced a disease progression
- developed an intolerable toxicity
- refused to continue on the study, or retrieved their consent
- were withdrawn from the study upon the investigator decision (e.g pregnancy, poor compliance, etc.)
- were withdrawn from the study upon the sponsor decision

For the patients who were withdrawn from the study for other reasons than disease progression (i.e.toxicity), tumor assessments as per RECIST criteria should be continued and documented every 6 weeks during 6 months from baseline and then every 9 weeks until disease progression or initiation of an antineoplastic treatment.

Common to all patients, whatever the treatment arm

One month (30 days) and two months (60 days) after end of treatment and on a quarterly basis thereafter:

- Disease and survival status: informations may be collected during visits or telephone calls.
- Clinical examination and vital signs
- Collection of persistent or long term occurring toxicities
- New antineoplastic therapies

On going toxicities or adverse event have to be monitored until resolution or returned to baseline level.
Adverse events must still be collected in the 30 days after the last investigational drug intake.
Any late Serious Adverse Drug Reaction (SAE related to the study drug), occurring at any time after the 30-day period must be reported to the R&D UNICANCER Safety Office.

Drug specific : durvalumab (+/-7 days)

At 30 days post-treatment ECOG performance status

- Hematology: haemoglobin, differential count, platelets
- Liver function tests : ASAT, ALAT, ALP, GGT, total bilirubin. **Note that** : if total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
- Biochemistry: sodium, potassium, calcium, magnesium, glucose, bicarbonate, chloride, urea, creatinine, total protein, albumin, amylase, lactate dehydrogenase, uric acid.
- Thyroid function tests: TSH, fT4, fT3

At 60 days post-treatment and at 3 months post-treatment

- ECOG performance status
- Heatology: haemoglobin, differential count, platelets
- Liver function tests : ASAT, ALAT, ALP, GGT, total bilirubin. **Note that** : if total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
- Biochemistry: sodium, potassium, calcium, magnesium, glucose, bicarbonate, chloride, urea, creatinine, total protein, albumin, amylase, lipase, lactate dehydrogenase, uric acid.

At 12 months post-treatment

- Hematology: haemoglobin, differential count, platelets

10.6.2. For non-randomized patients

Non randomized patients are those that are not eligible for randomization in any substudy because they:

- experienced disease progression at any time during chemotherapy or before randomization or didn't achieve at least 4 full cycles of chemotherapy because of toxicity (except when patient is currently under the first line treatment and is progressing or discontinuing treatment because of toxicity reasons during the first 4 cycles, a second line treatment can be initiated before randomisation)
- present at least one exclusion criteria or didn't achieve all the inclusion criteria in both substudies
- receive a decision from the Molecular Tumor Board contraindicating the randomization in any substudy

Few follow-up information will be collected for these patients during 24 months after the date of inclusion in the screening phase:

- treatments received and responses to the treatments
- disease and survival status at 24 months

11. SAMPLE SIZE DETERMINATION AND STATISTICAL CONSIDERATIONS

11.1. Sample size

11.1.1. Sample size substudy 1

The primary objective of the SAFIR02 lung study is to demonstrate that targeted maintenance with a targeted guided by the genomic analysis (arm A) improves progression-free survival as compared to maintenance therapy not guided by the genomic analysis (arm B). The primary endpoint is progression-free survival.

Assuming exponential survival, in order to detect an increase in median progression-free survival from 4 to 6 months (a hazard ratio of 0.66) with 80% power at a two-sided significance level of 0.05 using the logrank test and a 2:1 randomization (arm A: arm B), 205 events are required. Assuming a 72 months enrollment period with uniform accrual, and an additional 12 months follow-up, a total of 230 patients need to be randomized.

11.1.2. Sample size substudy 2

The primary objective of immune substudy 2 is to demonstrate that maintenance with immunotherapy (durvalumab, arm A2) improves progression-free survival as compared to a standard maintenance therapy (arm B2). The primary endpoint of the immune substudy 2 is also progression free survival.

Assuming exponential survival, in order to detect an increase in median progression-free survival from 4 months (Arm B2: Standard) to 6.5 months (Arm A2: “Anti-PD-L1”), corresponding to a hazard ratio of 0.62, with 80% power at a two-sided significance level of 0.05 using the logrank test and a 2:1 randomization (arm A2: arm B2), 155 events are required. Assuming a 54 months enrolment period with uniform accrual, and an additional 5.5 months follow-up, a total of 180 patients need to be randomized.

Based on the study progress and on the estimated number of patients not eligibible to the Substudy 1 randomisation phase, the objective of 180 patients randomized in the Substudy 2 can be achieved based on the planned 1350 screened patients.

11.2. Statistical analysis

11.2.1. Analysis Populations

For each substudy, analysis of the main efficacy criteria will be performed using the intent-to-treat (ITT) population, which is defined as the population of all randomized patients analyzed in the treatment group they were assigned to.

Patients who receive any amount of study treatment will be included in safety analyses. Safety results will be summarized by the treatment patients actually received.

Separate statistical analyses will be performed for substudy 1 and 2.

11.2.2. Baseline data

Continuous variables will be summarized by arm, using median, mean, standard deviation, minimum, maximum and number of available observations. Qualitative variables will be summarized by arm using: counts, percents, number of missing data.
Differences between arms will be assessed using Chi-square or Fisher’s exact test for qualitative variables and the t test or Mann-Whitney for continuous variables.

11.2.3. Primary endpoint

Primary endpoint will be analyzed on the ITT population when the required number of events has been reached.
For each substudy, the primary endpoint analysis will be a Cox regression analysis, adjusted for the factors that were used as stratification variables in the randomization, to compare the progression-free survival between the two treatment arms.

The Kaplan-Meier approach will be used to estimate survival rates for each treatment arm. A Cox proportional hazards model adjusted will be used to estimate the hazard ratio (HR) between the two treatment arms (ie, the magnitude of treatment effect) and its 95% confidence interval (CI).
In an exploratory analysis, additional prognostic covariates (clinicopathological factors and the molecular aberrations identified during the screening phase) will be added to the Cox proportional hazards regression models.
For substudy 1, each indidivual experimental drug will be compared separately to standard maintenance in an exploraty fashion in a Cox regression model including only those patients that were oriented to that particular drug by the MTB.

11.2.4. Secondary endpoints

Overall survival will be analyzed with the same methods as the progression-free survival analysis.
Objective response rate (e.g. Complete or partial response) will be assessed and described by arm. Comparison between groups will be performed using Chi-square or Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated by logistic regression after adjustment for the variables used as stratification factors in the randomization. Additional multivariate logistic regression models will be performed in an exploratory manner, to determine if adjustment for the additional prognostic covariates will modify the conclusions. Changes in tumor size over time will be analyzed using (non-)linear mixed models. For the exploration of the efficacy (response rate, changes in tumor size, progression-free survival, overall survival) of the individual targeted agents and the association between molecular anomalies and efficacy, logistic regression, Cox regression and (non-)linear mixed models will be used. Only those patients that were oriented to that particular drug by the MTB will be included in the latter analysis. If not enough patient are exposed to particular targeted agents, all the patients from the targeted substudy will be included and a random treatment by target interaction included in the model. Forest plots will be constructed to visualize the treatment effect of individual targeted agents together with interaction test results.

For the prospective pooled analysis of the SAFIR02 lung and SAFIR02 breast studies, a specific meta-analysis plan will be developed.

11.2.5. Safety analysis

Safety analysis will be performed on the safety population in substudy 1 and 2 separately.

Tolerability and safety will be assessed through recording of adverse events using NCI-CTCAE toxicity classification, monitoring biological, clinical and paraclinical parameters.
Each of the following will be assessed by cycle and by patient:

- AEs by toxicity grade
- SAEs
- Drug-related AE
- Treatment discontinuation due to study treatment
- Occurrence of AE with toxicity grade > 2

Frequency, percentage with 95% confidence interval will be computed for each event. For biological, clinical and paraclinical parameters, descriptive statistics will be produced for each visit, and change from baseline will be calculated.
For substudy 1, the satefy of each individual experimental drug will also be evaluated separately (and tabulated together with those patients that received standard maintenance therapy but were oriented to that particular drug by the MTB).

11.2.6. Interim safety analysis

An interim safety analysis will be carried out after the first 60 randomized patients in both studies of SAFIR02 program (Lung and Breast). Indeed, as there are 7 investigational drugs common to both studies, the safety data review will be performed considering patients randomized in both studies. Safety data will be transmitted to the IDMC (see section 12.3.2) for review.

A drug-specific interim analysis for futility may be planned for the study drugs that have been given most frequently to the patients randomized in the SAFIR02 LUNG trial. Boundaries will be fixed according to the O'Brien Fleming method assuming for each study drug a target hazard ratio of 0.66 on progression-free survival. The first futility analysis will concern selumetinib, and it the O'Brien-Fleming futility boundary is crossed, the IDMC may recommend to stop this drug in the rest of the SAFIR02 study.

12. SAFETY

12.1. Adverse Events

12.1.1. General definition

An adverse event is defined as any medical event, or any event requiring clinical investigation, occurring during treatment, whether or not it is attributable to the study drugs. (especially: abnormal biological exams, symptoms, new or impaired concomitant diseases…).
Any variation of the studied disease, excepted for serious impairment, is not considered an adverse event.
Any event occurring during the trial (from signature to one month after last study drug intake) must be reported in the case report form.

As far as possible, each AE should be evaluated to determine:

1. The severity grade (CTCAE grade 1-5)
2. Its relationship to each study drug (suspected/not suspected)
   The investigator must do his/her best to explain each adverse event and establish, when it exists, the connection with each trial's product.
   Causality will be established for each product as follows:
   - no, it is not related;
   - yes, there is a reasonable possibility of causality according to the following criteria:
     - the pharmacology of the product is known,
     - the effects are of similar nature compared to already known effects reported for this product or other products of the same family or category of compound,
     - adverse event already reported in the literature for similar products and being considered as related to the study product
     - adverse event tightly related to the treatment period (between the beginning of the administration – the drug challenge period – and the end of administration – dechallenge period) or positive rechallenge.
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken, non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined in section 12.2.

<u>Adverse events follow-up:</u>
Adverse events must be followed until they have resolved or stabilized.

12.1.2. Known adverse effects

The following adverse events have been reported to be likely associated with the corresponding study drug and are to be regarded as expected for regulatory reporting purposes.
Table 19 reports the summary of known adverse events. Investigator should refer to the IB for detailed information.

Table 19: known adverse events

Investigational Drug	Adverse Events
Vistusertib	*Very common:* fatigue/lethargy/asthenia, diarrhea, nausea, vomiting, stomatitis/mucositis, rash, hypokalaemia, hypophosphataemia, hyperglycemia, decrease appetite. *Uncommon* : haematological effects, cardiac repolarization changes, non infectious pneumonitis
AZD4547	Alopecia, blood creatinine increased, diarrhoea, dysguesia, epithelial and mucosal dryness, hair and eyelash disorders, hyperphosphataemia, nail disorder, RPED (reported as chorioretinopathy, detachment of macular retinal pigment,epithelium, detachment of retinal pigment epithelium, retinal detachment), stomatitis, transaminases increased.
AZD5363	*Very common :* Diarrhea, rash, hyperglycemia, stomatitis, decreased appetite, nausea, vomiting *Common :* hypersensitivity , dry skin, pruritus
AZD8931	Diarrhea, Stomatitis, rashes, dry eye/conjunctivitis, dry skin, decline in LVEF
Selumetinib (AZD6244)	*Very common :* rash, dry skin, diarrhea, nausea, vomiting, asthenia, peripheral oedema, facial oedema, pyrexia, dyspnea, hyperphosphataemia, increased blood pressure, transaminase elevation, hypoalbuminaemia, reduced LVEF. *Common* : paronychia, stomatitis/mucositis, dry mouth, blurred vision, calcium x phosphate product elevation, creatinine kinase increased. Not calculable to date : Central Serous Retinopathy / RPED, retinal vein occlusion Neutropenia, severe reductions in neutrophil count and interstitial lung disease have been reported in patients receiving selumetinib in combination with docetaxel. Large intestine perforation with fatal outcome has been reported in 2 patients receiving selumetinib in combination with gemcitabine/cisplatine doublet chemotherapy. Based on the current available information a causal association between the events and the administration of selumetinib cannot be established.
Vandetanib (Caprelsa®, ZD6474)	Very commun: diarrhoea, nausea, vomiting,abdominal pain, fatigue, asthenia, appetite decreased, hypocalcaemia, insomnia, rash and other skin reactions (including acne, dry skin, dermatitis, pruritis), photosensitivity reaction, headache, hypertensionCommun: prolongation of ECG QT interval, stomatitis, dry mouth, weight decreased, increase of serum ALT and AST, dehydration, hypothyroidism, depression, proteinuria, nephrolithiasis, hematuria, epistaxis, palmar-plantar erythrodysaesthiesia syndrome, alopecia, nail disorders, vision blurred, corneal opacity, conjunctivitis, dry eye, visual impairment, dysgeusia, ischemic cerebrovascular conditions, hypertensive crisis Uncommon: heart failure, acute heart failure, pancreatitis, increased haemoglobin, Stevens–Johnson syndrome, toxic epidermal necrolysis

Olaparib (Lynparza®, AZD2281)	*Very common* : decreased appetite, headache, dysgeusia, dizziness, nausea, vomiting, diarrhoea, dyspepsia, fatigue/athenia, anemia, neutropenia. *Common*: stomatitis, upper abdominal pain, thrombocytopenia, leukopenia, rash and increase in creatinine. Uncommon: lymphopenia, hypersensitivity, dermatitis and mean corpuscular volume elevation Important potential risks: myelodysplastic syndrome/ acute myeloid leukemia (<1% of patients), pneumonitis(<1% of patients), new primary malignancies
Savolitinib	Very common : fatigue, nausea, vomiting, peripheral oedema, elevations of liver enzymes and drug induced liver injury. Common : drug-related pyrexia Uncommon : hypersensitivity
Vemurafenib	Risk described for vemurafenib Very common: cutaneous squamous cell carcinoma of the skin, seborrheic keratosis, skin papilloma, decreased appetite, headache, dysgeusia, cough, diarrhoea, vomiting, nausea, constipation, photosensitivity reaction, actinic keratosis, rash, rash maculo-papular, rash papular, pruritus, hyperkeratosis, erythema, alopecia, dry skin, sunburn, arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain, fatigue, pyrexia, oedema peripheral, asthenia, GGT increase Common: folliculitis, basal cell carcinoma, new primary melanoma, 7th nerve paralysis, dizziness, uveitis, palmar-plantar erythrodysaesthesia syndrome, panniculitis (including erythema nodosum), keratosis pilaris, arthritis, ALT increase, AST increase, alkaline phosphatase increase, bilirubin increase, weight decreased, QT prolongation, blood creatinine increased, abnormal creatine phosphokinase related to muscle breakdown. Uncommon: non-cutaneous squamous cell carcinoma, neutropenia, neuropathy peripheral, retinal vein occlusion, vascular disorders pancreatitis, liver injury, toxic epidermal necrolysis, Stevens-Johnson syndrome, Rare: chronic myelomonocytic leukaemia, pancreatic adenocarcinoma, drug reaction with eosinophilia and systemic symptoms (DRESS), acute interstitial nephritis, acute tubular necrosis Potentiation of radiation toxicity: Radiation recall and radiation sensitization have been observed from post-marketing sources. However the frequency of this adverse reaction is unknown since radiation treatment information including radiation dosage information is not routinely collected in spontaneous safety reports.
Cobimetinib	Very Common : anaemia, serous retinopathy, blurred vision, hypertension, haemorrhage, diarrhoea, nausea, vomiting, photosensitivity, rash, rash maculo-papular, dermatitis acneiform, hyperkeratosis, pyrexia, chills, blood creatinine phosphokinase increased, ALT increased, AST increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased

	Common : basal cell carcinoma, cutaneous squamous cell carcinoma, keratoacanthoma, dehydration, hypophosphataemia, hyponatremia, hyperglycaemia, visual impairment, pneumonitis, ejection fraction decreased, blood bilirubin increased
Durvalumab (MEDI4736)	Very commun: diarrhoea, rash, pruritus, pyrexia, oedema peripheral, upper respiratory tract infections, cough/productive cough, abdominal pain Commun: pneumonitis, ALT increased/AST increased, colitis, hypothyroidism, hyperthyroidism, blood creatinine increased, infusion related reaction, night sweats, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, dysphonia, blood TSH increased, blood TSH decreased, dysuria Uncommun: hepatitis, adrenal insufficiency, dermatitis, myositis, interstitial lung diseaseILD, nephritis Rare: hypophysitis/hypopituitarism, type 1 diabetes mellitus, diabetes insipidus, nephritis, myocarditis, polymyositis

The following terms are used to rank the undesirable effects by frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) including isolated reports.

For standard maintenance drugs, refer to Summary of Product Characteristics for known adverse events description.

12.1.3. Guidelines for management of toxicities

12.1.3.1. Stomatitis/Oral Mucositis/Mouth Ulcers

Investigational drugs at risk: vistusertib, AZD4547, AZD8931, vandetanib, selumetinib, AZD5363, olaparib, savolitinib (potentially).

As a class effect of mTOR inhibitors, mucosal inflammation/stomatitis have occurred commonly in patients receiving vistusertib as monotherapy.
Events of stomatitis/oral mucositis and dry mouth are expected events with AZD4547, AZD8931, selumetinib, vandetanib, savolitinib and olaparib.

Following guidelines should be followed for any patient who develops stomatitis/mucositis.
• For mild toxicity (Grade 1), use conservative measures such as non alcoholic mouth wash or salt water (0.9%) mouth wash several times immediately after drug administration (1-3h) and during the day as required until resolution.

• For more severe toxicity (Grade ≥ 2), the suggested treatment includes dexamethasone based mouthwashs with 10 ml of commercially available 0.5 mg/5 ml dexamethasone oral solution to swish x 2 min. In addition, topical analgesic mouth treatments (i.e., local anaesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenolic compoundsmay be used. Importantly, patients must be instructed to swish and expectorate the mouth rinse to avoid systemic exposure to dexamethasone. Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid these agents.

• For Grade 3 stomatitis/oral mucositis/mouth ulcers, systemic pain killers are indicated (e.g. oral or s.c. morphine).

12.1.3.2. Hyperglycemia

Drugs at risk : vistusertib, AZD5363, cobimetinib, durvalumab.

For durvalumab, refer to Section 12.1.3.16 for type I diabetes mellitus.
For vistusertib and AZD5363, mTOR kinase and AKT are known to be involved in the regulation of glucose metabolism (Soliman 2005, Whiteman et al 2002), and therefore glucose and insulin elevations are expected and consistent with the primary pharmacology of both compounds.

In case of hyperglycemia, study drugs dose adjustments should be followed as described in section 0 to minimize metabolic risks, allow patients to continue receiving the same dose of investigational drug where possible, and avoid compliance issues.

Following guidelines should be followed for any patient who develops hyperglycemia.
For Grade 1 (FPG < 8.9 mmol/L (160mg/dL)) : no action
For Grade 2 (8.9≤FPG<13.9 mmol/L (160mg/dL-250mg/dL)) : consider oral metformin* and appropriate medical management of metabolic disturbances as per local guidelines
For Grade 3 (13.9≤FPG<27.8 mmol/L (250mg/dL-500mg/dL)): consider oral metformin* and appropriate medical management of metabolic disturbances as per local guidelines, hospitalization is indicated.
For Grade 4 (FPG>27.8 mmol/L (500mg/dL)) : in the case of patients developing severe hyperglycaemia, patients may require treatment in an intensive care unit. Aggressive management of metabolic disturbances as per local guidelines in indicated.
Due to the predicted short half-life of investigational product (vistusertib and AZD5363), only a short period of insulin resistance is expected. Therefore early treatment with high doses of insulin should be carefully evaluated and blood sugars monitored as per standard clinical practice.

Note that : *Metformin is recommended for the management of hyperglycemia occurring in patients treated with AZD5363 or vistusertib. Investigators should exercise caution in the dosing and management of patients receiving the metformin/AZD5363 or vistusertib combination and must be vigilant for signs of renal impairment and metformin toxicity, such as lactic acidosis and hypoglycemia, namely: lethargy, hypotension, poor urine output, drowsiness, irritation, tachypnea, sweating, diarrhea, and vomiting.
Patients should attend for clinical assessment when taking both AZ5363 or vistusertib and metformin concurrently, including monitoring of serum creatinine at least once per week for the first 3 weeks after initiation of metformin, then every 3 weeks thereafter.
Metformin should only be given on the days when AZD5363 is also given, i.e 4 days in a week, (the half-life of AZD5363 is approximately 8-15 hours), and should be withdrawn when treatment with AZD5363 is also withdrawn, unless otherwise clinically indicated.

12.1.3.3. Pulmonary toxicities

INTERSTITIAL LUNG DISEASE/ PNEUMONITIS

Investigational drugs at risk : vandetanib, durvalumab
Potentially at risk: selumetinib, AZD8931, vistusertib, cobimetinib and olaparib.

ILD or pneumonitis has been observed with vandetanib and deaths have been reported.
There have been reports of pneumonitis-type events (including interstitial lung disease) in a small number of patients with advanced NSCLC receiving treatment with selumetinib in combination with docetaxel. An association between selumetinib and ILD has not been established due to the presence of confounding features including pneumonia, progression of thoracic metastatic disease, history of thoracic radiation or concomitant medications.

Important potential risks based on the mechanism of action of durvalumab and its related molecules include immune-mediated reactions such as pneumonitis. Immune-mediated reactions reactions are outlined in 12.1.3.16.

Interstitial lung disease, including interstitial pneumonitis, which may be acute in onset, has been observed infrequently (<1.5%) in patients treated with EGFR-tyrosine kinase inhibitors, such as erotinib. As a possible class effect, AZD8931 is potentially at risk of ILD events, although no such event has occurred to date.

Pneumonitis is an uncommon event with vistusertib, but as it is reported as a possible class effect of mTOR inhibitors with an incidence of 5%-36%, appropriate monitoring of patients has to be performed.
Pneumonitis has been reported in <1.0% patients treated with olaparib monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy).

Pneumonitis has also been reported in patients treated with cobimetinib.

Following guidelines should be followed for any patient who develops signs or symptoms of interstitial lung disease / pneumonitis.
A high resolution CT scan and a complete pulmonary function test should be performed according to local standards, as clinically indicated. The test will include the highest of 3 forced expiratory volumes, forced vital capacity, and carbon monoxide diffusing capacity (DLCO% & DLCO). A recent haemoglobin measurement should also be available at the time of the DLCO evaluation.

For any new respiratory symptoms (cough, dyspnea, lower respiratory infection) not clearly explained by other factors (eg, dyspnea associated with substantial drop in hemoglobin), patients should have oxygen saturation measured. If <92%, the high resolution CT scan of the chest should be repeated and pulmonary function tests should be performed.

DYSPNEA

Investigational drugs a risk : selumetinib, potentially: olaparib

New or worsening dyspnea has been reported commonly during treatment with selumetinib and could potentially occur with olaparib. Investigation to determine the underlying cause is recommended and study drug interruption or reduction is considered as presented in Figure 9.

12.1.3.4. Severe fatigue

Investigational drugs at risk : vistusertib, selumetinib and savolitinib

Following guidelines should be followed for any patient who develops severe fatigue.
In cases of severe fatigue (grade ≥ 3), cardiovascular parameters, vital signs including supine and standing BP and HR, and ECGs should be re-assessed, together with lab parameters including venous lactate, to address underlying causes such as metabolic acidosis (electrolytes [Na, K, Cl] and HCO3), with calculation of anion gap using the following formula:

Subtract the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium and potassium (cations):
= ([Na+] + [K+]) − ([Cl−] + [HCO3−])

12.1.3.5. Cardiac toxicities

ECG FINDINGS

a)-General ECG guidelines

ECGs will be evaluated by suitably qualified personnel for the presence of QTc prolongation or other abnormalities, in particular, any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia. Any clinically significant abnormal findings or QTc prolongations will be recorded as AEs. If present, the clinical signs and symptoms associated with the abnormal finding should also be reported as the AE with the ECG abnormality given as explanatory information.

An ECG should be performed at any cardiac event with symptoms that may be due to cardiac ischemia, or arrhythmia (such as chest pain or palpitations). An ECG will also be captured in all cases of dyspnea ad pulmonary edema and additionally at the discretion of the investigator if clinically indicated.

12-lead ECG will be obtained after the patient has been resting semi-supine for ≥10 minutes prior to times indicated. All ECGs should be recorded with the patient in the same position. Triplicate ECG recordings **should be performed within a 10 min interval** and will be taken **for all requested ECG measurements in**

the protocol A standardized ECG machine should be used and the patient should be examined using the same machine throughout the study.

b)-Repolarization changes

Investigational drugs at risk : vistusertib, vandetanib

Clinically non-significant cardiac repolarisation abnormalities, T-wave flattening and T-wave inversions have been observed retrospectively during routine ECG reviews with Vistusertib, these changes have not been associated with cardiac signs or symptoms. The mechanism and the clinical significance of these changes are unknown, although no clinical events related to left ventricular function or arrhythmia have been recorded. These events will be closely monitored and further investigated (refer to the vistusertib specific flow-chart, appendix 1).
Vandetanib produces repolarization abnormalities in human myocardium that are consistent with blockade of the I_{KR} (potassium) channel. The most consistent electrophysiologic effects are a change in T-wave morphology (flattening, broadening or notching) and prolongation of the QT interval.

Following guidelines should be followed for any patient who develops persistent, confirmed T wave repolarization abnormalities (inversion or flattening) on regularly scheduled ECGs. They should have :
-a triplicate ECG every other week through the first 10 weeks of treatment, then monthly, or as clinically indicated.
-a follow up LVEF determined using the same technology used at baseline (ECHO or MUGA) approximately 2 weeks after the T wave abnormality is first recorded, and then as clinically indicated
-a troponin measurement within 24h, and then as clinically indicated.
All of these examinations should be repeated after treatment discontinuation for assessment of reversibility. If the abnormality is still detected, assessment should be pursued until recovery, as clinically indicated.

c)-QTc prolongation

Investigational drugs at risk : vandetanib, potentially for AZD8931, AZD5363 and vemurafenib

The dose modification schedules provided in section 0 should be strictly followed in cases of QTc prolongation.
Following guidelines should be followed for any patient who develops QTc prolongation.
Triplicate ECG measurements will be performed within a 10 min interval and will be obtained for each requested ECG in the study. The QTc value will be obtained by calculating the average QTc value from the 3 measurements.
If QTc >480 msec, study therapy is maintained at the same dose level, electrolytes and concomitant medications are assessed and corrected as appropriate.
In case of prolonged QTc (>500 msec), the ECG should be manually reviewed by a suitable qualified personnel at the site to confirm the QTc prolongation. If the manual lecture confirms the QTc prolongation, the study therapy should be withheld until the drug relationship of the event is determined (rule out electrolyte imbalance or influence of concomitant medication). In case of a study treatment related QTc interval measurement higher than 500 msec (grade ≥3) dosing should be interrupted and permanently discontinued for a Grade 4 QTc prolongation event. In both circumstances (Grade 3 or 4) continuous ECG monitoring (ECG and electrolytes 3 times a week) will be done under physician supervision until the QTc value recovers to a value <480 msec and cardiologist advice.
When study drug is restarted due to Grade 3 prolongation of the QTc, **triplicate ECG surveillance** will again be performed on a schedule similar to the one used at the start of the study, as described in section 12.1.3.5.

Serum potassium, magnesium and calcium should be maintained within normal limits to decrease the risk of ECG QTc prolongation. Additional surveillance of QTc, electrolytes and renal function is especially required if diarrhea, diarrhea worsening / dehydration, electrolytes imbalance and / or renal failure. If a QTc increase is observed but remains below 500 msec, a cardiologist must be consulted.

The concomitant use of medications generally accepted as **having a risk** of causing Torsades de Pointes (refer to Appendix 8 – Drugs at risk of Torsades de Pointes or Arizona CERT website http://www.crediblemeds.org/healthcare-providers/drug-list/) with study drugs at risk of QTc prolongation are not allowed within 2 weeks (or more) of randomization or during the study. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

Co-administration of drugs that in some reports might be associated with Torsades de Pointes (identified as of possible or conditional risk) should be avoided to extend of possible during the study. However, these drugs can be allowed, at the discretion of the investigator**, if considered absolutely necessary**. In such cases, the patient must be closely monitored, including ECG and electrolytes within 24 hours of commencing the concomitant medication, and then at least weekly checks for QTc and electrolytes while the patient remains on the medication. The frequency of ECG and electrolytes could revert to the study standard schedule if no QTc prolongation has been noted during 4 weeks of co-administration.

DECREASE IN LEFT VENTRICULAR EJECTION FRACTION

Investigational drugs at risk : selumetinib, potentially AZD8931, cobimetinib and savolitinib (potentially)

Echocardiography is the preferred modality for the measurement of LV systolic function because of the additional information it provides and the avoidance of ionizing radiation. MUGA scanning is an alternative where there are patients or intuitional factors that make echocardiography impractical.
Whatever the chosen modality at baseline, LVEF should be assessed with the same technics throughout the study for one patient. It is also strongly encouraged that the same laboratory and operator perform the procedure for each individual patient.

Following guidelines should be followed for any patient who develops LFEV decrease:
Decline ≥ 15% and LVEF ≥ 50%, repeat echocardiography or MUGA in 3 weeks, and if stable consider 3-monthly LVEF.
Decline ≥ 10% and LVEF 49-40%, monitor every 3 weeks and seek for cardiology review. Consider ACE inhibitor if appropriate. If LVEF is stable, consider 6-weekly echo or MUGA.
Decline ≥ 10% and LVEF < 40%, monitor every 3 weeks and seek for cardiology review. Consider ACE inhibitor if appropriate.

12.1.3.6. Hyperphosphatemia

Investigational drugs at risk : AZD4547, selumetinib

The cardiac mineralization identified in pre-clinical species is thought to be as a direct consequence of elevated serum phosphate levels due to pharmacological effect of AZD4547 on phosphate homeostasis in the kidney. However, there have though been no reports, and no evidence of any soft tissue, including cardiac, mineralization clinically. The potential risk is based upon presumption that increases in phosphate precede mineralization. Therefore, specific cardiac surveillance with AZD4547 should be strictly followed to detect cardiac functional changes (refer to AZD4547 schedule in Appendix 1 – Flow chart).
Small increases in serum phosphate levels to above the normal range have been reported in patients receiving selumetinib. Persistent elevation in calcium x phosphate product above 4.5 $mmol^2/L^2$ has occurred very rarely, and resolution on continuing selumetinib administration with sevelamer hydrochloride (Renagel®) treatment was reported.

Any patient who experiences a doubling of phosphate from baseline or a corrected calcium x phosphate product > 4.5 $mmol^2/L^2$ may remain on study treatment but phosphate chelation therapy (non-calcium containing agent) should be initiated, and clinical chemistry monitored weekly until resolution of the parameter to below the intervention limit. Investigators must seek appropriate specialist medical consultation (renal or metabolic) to advise on the prescription and titration of phosphate chelation agents and to raise the patients awareness of low phosphate diets.

12.1.3.7. Hepatotoxicity

Investigational drugs at risk : selumetinib (mild), vandetanib, AZD4547 (mild), savolitinib, vemurafenib+cobimetinib and durvalumab

Drug-induced liver injury during study treatment is considered a medically important event, regardless of whether hospitalization is required or not. It is defined as an AST or ALT result in excess of 10x ULN, or AST

or ALT in excess of 8xULN in combination with a doubling of bilirubin from baseline, which is considered to be related to study drug.
The dose modification schedule provided in
Appendix 9 – Guidance on management of hepatotoxicity should be strictly followed in cases of suspected or confirmed drug-induced liver injury, except for durvalumab for which guidelines given in Section 0 should be applied.

If a drug-induced liver injury is suspected:

- immediately and permanently discontinue suspected agents,
- complete the SAE form and promptly report to the R&D UNICANCER safety Office (refer to section 12.2.5),
- complete the drug-induced liver injury specific form in the CRF,
- the patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include:
    - Laboratory tests, detailed history, physical assessment and the possibility of hepatic neoplasia (primary or secondary) should be considered.
    - In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase.
    - A detailed history, including relevant information, such as review of ethanol, acetaminophen (paracetamol), recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected on the drug-induced liver injury specific form in the CRF.
    - If possible, an acetaminophen (paracetamol) level should be obtained in all patients with suspected drug-induced liver injury at the time of presentation regardless of their history of acetaminophen (paracetamol) use.
    - Further, testing for acute hepatitis A, B, C, or E (if possible) virus infection, including testing for reactivation of viral infection (HBV), should be considered.
    - Additional serologies (Epstein Barr virus cytomegalovirus, herpes simplex virus, varicella zoster virus, parvovirus B19, toxoplasma) should be considered.
    - Liver imaging to rule out biliary obstruction and assess the extent of metastatic liver disease should be considered as well.

12.1.3.8. Ophthalmic toxicities

Investigational drugs at risk : AZD4547, selumetinib, AZD8931 (mild), vandetanib (mild), savolitinib (potentialy) and vemurafenib + cobimetinib.

It is anticipated that patients treated with drugs at risk will report any visual disturbances or discomfort relating to the eye in advance of any significant pathology such as ulceration occurring.
Approved agents which inhibit EGFR/ErbB1 like erlotinib have been associated with reports of ophthalmic toxicity (e.g. conjunctivitis, dry eye). AZD8931 and vandetanib have an expected ophthalmic safety profile associated with EGFR inhibitors. Both compounds cause infrequent, mild and reversible ophthalmic adverse events.

RPED has been identified in clinical studies with AZD4547. The prognosis is generally good if there is no actual haemorrhage from the capillaries and no evidence of any fibrovascular growth in the sub-RPE space. The majority of these events of RPED and other posterior eye changes were diagnosed after 21 days of treatment.
Adverse events consistent with central serous retinopathy or retinal vein occlusion have been reported in a small number of patients receiving treatment with selumetinib.

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including cobimetinib. The majority of events were reported as chorioretinopathy or retinal detachment.
Median time to initial onset of serous retinopathy events was 1 month (range 0-9 months). Most events observed in clinical trials were resolved, or improved to asymptomatic Grade 1, following dose interruption or reduction.

Serious ophthalmologic reactions including uveitis have been reported with vemurafenib.

Conjunctivis is a potential risk with savolitinib.

If patients experience toxicities regarding the anterior aspect of the eye (dry eyes, punctuate keratopathy and keratitis) such events must be clinically managed to prevent secondary consequences eg, secondary infections following corneal abrasions. Lubricating eye drops/replacement tears should be used; if there is any indication of extra eyelash growth or eyelashes rubbing on the cornea then these eyelashes should be removed. The decision to continue on study treatment if mild corneal changes in the eye examination are observed will be left to the Investigator's discretion, since a patient may indicate a wish to tolerate minor discomfort if there is perceived clinical benefit from the therapy. A patient should also be immediately withdrawn from treatment if corneal ulceration occurs, and appropriate expert ophthalmologic consultation should be initiated.

Any patient who experiences any of the following at any time requires an ophthalmic assessment:

- abnormalities in the Amsler grid test
- changes in near vision acuity
- blurred vision
- distortion of central vision

Ophthalmic assessments should include the following, in the order stated:

- visual acuity (best corrected) including near and far vision for each eye separately
- Amsler grid
- Schirmer's test without anesthesia –read after 5 minutes (this test should be done before instillation of stains or dilatory agents)
- Slit lamp examination
    - Apply 1 drop of 2% fluorescein followed by 1 drop of normal saline
    - Apply Lissamine Green (only applicable if used as a local practice)
    - Measure intra-ocular pressure
    - Photograph any abnormalities
- Fundoscopy and lens examination following pupil dilatation should be performed using binocular equipment and a 78-dioptre lens (or nearest available equivalent lens)

OCT scans should be performed on the occurrence of clinical symptoms or signs suggestive of:

- RPED occurring with AZD4547 (OCT scan diagnostic of RPED should be managed according to the algorithm included in figures 6 and 7). OCT is the preferred methodology for diagnosis of RPED. If OCT is not available as part of local clinical practice, an equivalent alternative diagnostic methodology to screen for RPED should be used.
- RPED, Central serous retinopathy (CSR) or retinal vein occlusion (RVO) occurring with selumetinib or cobimetinib (diagnosis of CSR and RVO should be managed according to algorithm included in figure 8)
- Any other visual disturbance if clinically justified upon the judgement of the investigator

12.1.3.9. Diarrhea

Investigational drugs at risk : all

It is recommended that treatment-induced diarrhea should be carefully monitored and aggressively treated to ensure that severe complications (QTc prolonged due to unbalanced electrolytes) are avoided and that study treatment is not delayed.

- *For **uncomplicated Grade ≤2 diarrhea**, are recommended*:

Dietetic measures: Stop all lactose-containing products, drink 8 to 10 large glasses of clear liquids per day, eat frequent small meals, recommend low fat regimen enriched with rice, bananas, and apple sauce.

Pharmacological treatment: Administer loperamide: initial dose 4mg, followed by 2mg every 4 hours or after every unformed stool, consider continuation of loperamide until diarrhea-free for 12h, consider electrolyte replacement, as appropriate.

If after 12 hours of loperamide treatment the diarrhoea is not improving or resolved, the patient should be instructed to contact the centre and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg

every 4 hours at night) and continue to take loperamide until they have been free from diarrhoea for at least 12 hrs. Additional treatment may be considered according to local practice.

- *For **any Grade uncontrolled or diarrhea Grade ≥3 or any Grade with complications** (dehydration, fever and/or Grade ≥3 neutropenia) are recommended:*

Dietetic measures: As per Grade ≤2 diarrhea

Pharmacological treatment: As per Grade ≤2 diarrhea; If dehydration is severe, administer octreotide and use intravenous fluids as appropriate; Consider prophylactic antibiotics, especially if diarrhea is persistent beyond 24h or there is a fever or Grade 3-4 neutropenia; Consider electrolyte replacement, as appropriate.

12.1.3.10. Skin and nail reactions

Investigational drugs at risk : vistusertib ~~AZD2014~~, AZD5363, AZD8931, selumetinib, vandetanib, AZD4547, olaparib, savolitinib, vemurafenib + cobimetinib and durvalumab.

For durvalumab, refer to Section 12.1.3.16 for immune-mediated dermatitis.

Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) has been reported in association with vemurafenib. In patients who experience a severe dermatologic reaction, vemurafenib treatment should be permanently discontinued

General dermatological guidance

It is strongly recommended that all patients exposed to drugs at risk of photosensitivity reactions follow a program of sun-protective measures while receiving study treatment and for 3 to 4 weeks after discontinuing study treatment. For vistusertib and AZD5363, the program of sun-protective measures should be prolonged up to 3 months after vistusertib or AZD5363 discontinuation.The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study treatment.

During the study, patients should use sunglasses and sunscreen (SPF ≥30), reapplied as necessary on areas of skin directly exposed to sunlight.

Investigators may consider issuing patients with a prescription for topical treatments, used at their discretion. However, topical or oral steroids should not be implemented prophylactically and treatment should only be started once confirmed with the investigator.

Patients must notify the study site immediately if any kind of skin rash develops, and they should obtain study site approval before using any prescribed topical treatments. They should also be instructed to contact the site if the rash changes (e.g. if it spreads or becomes painful).

It may be beneficial to warn patients to avoid skin products which may cause irritation (e.g., perfumed soaps or products containing retinol or retinoic acid). Camouflage make-up (non-comedogenic or non-pore blocking) may be used during study treatment.

Use of skin moisturizer (thick, alcohol-free) at bedtime is recommended in patients receiving drugs at risk.

MACULO-PAPULAR RASH

*For **Grade 1:*** <10% body surface area (BSA) covered with macules/papules; with or without symptoms (e.g.,pruritus, burning, tightness), are recommended:

- Topical steroid moderate strength* bid
- Oral antihistamine (if symptomatic)

*For **Grade 2***: 10% to 30% BSA covered with macules/papules; with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living (ADL) are recommended:

- Topical steroid moderate strength bid
- Oral antihistamine (if symptomatic)

*For **Grade ≥3:*** >30% BSA covered with macules/papules; with or without associated symptoms; limiting self care ADL, is recommended:

- Oral steroid for up to 2 weeks.

ACNEIFORM / PAPULOPUSTULAR RASH

*For **Grade 1:*** <10% body surface area (BSA) covered with papules/pustules; with or without symptoms of pruritus or tenderness, are recommended:

- Topical steroid moderate strength* bid
- Topical antibiotic* bid or Oral antibiotic* for 6 weeks

*For **Grade 2***: 10% to 30% BSA covered with papules/pustules; with or without symptoms of pruritus or tenderness; psychosocial impact; limiting instrumental activities of daily living (ADL) are recommended:

- Topical steroid moderate strength* bid
- Oral antibiotic for 6 weeks if topical antibiotics are being used

*For **Grade ≥3:*** >30% BSA covered with papules/pustules; with or without symptoms of pruritus or tenderness; limiting self care ADL, associated with local superinfection:

- Topical steroid moderate strength* bid
- Oral antibiotic for 6 weeks. Switch to broad spectrum/gram negative cover if infection suspected (yellow crusts, purulent discharge, painful skin/nares); consider skin swab for bacterial culture.

DRY SKIN / XEROSIS

*For **Grade 1:*** <10% body surface area (BSA); No associated erythema or pruritus, are recommended:

- Face: over-the-counter moisturizing cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid

*For **Grade 2***: 10% to 30% BSA; Associated with erythema or pruritus; limiting instrumental activities of daily living (ADL) are recommended:

- Face: over-the-counter moisturizing cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid

*For **Grade ≥3:*** >30% BSA; Associated with erythema or pruritus; limiting self care ADL; are recommended:

- Face: over-the-counter moisturizing cream or ointment bid
- Body: ammonium lactate 12% cream bid or salicylic acid 6% cream bid
- Eczematous areas of body: topical steroid moderate strength* bid

PRURITUS

*For **Grade 1:*** Mild or localized, is recommended:

- Topical steroid moderate strength* bid or topical antipruritic* bid

*For **Grade 2***: intense or widespread, intermittent, skin changesfrom scratching (eg,oedema, papulation, excoriation, lichenification, oozing/crusts), limiting instrumental ADL are recommended:

- Topical steroid moderate strength* bid or topical antipruritic* bid
- Oral antihistamine*

*For **Grade ≥3:*** intense or widespread, limiting self-care ADL or sleep; are recommended:

- Oral antihistamine*

• GABA agonist (gabapentin 300 mg or pregabalin 50-75 mg every 8 hours) or doxepin (25-50 mg every 8 hours)

PARONYCHIA

*For **Grade 1:*** Nail fold oedema or erythema; disruption of the cuticule; is recommended:

• Topical antibiotic* bid and vinegar soaks in a 1:1 solution of white vinegar in water for 15 minutes every day.

*For **Grade 2***: Nail fold oedema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL; are recommended:

• Topical antibiotic* bid and vinegar soaks in a 1:1 solution of white vinegar in water for 15 minutes every day.

• Topical silver nitrate weekly.

*For **Grade ≥3:*** limiting self-care ADL; are recommended:

• Topical antibiotic* bid and vinegar soaks in a 1:1 solution of white vinegar in water for 15 minutes every day.

• Topical silver nitrate weekly.

• Consider nail avulsion/removal.

*Example topical steroids, antipruritics and antibiotics:

- Topical steroids moderate strength: Triamcinolone acetonide 0.025%; Desonide 0.05%; Fluticasone proprionate 0.05%; Aclometasone 0.05%
- Oral antihistamines: Diphenhydramine 25-50 mg every 8 hours or Hydroxyzine 25 mg every 8 hours or Fexofenadine 60 mg every 8 hours
- Oral steroids: Predinosolone: 5 mg to 60 mg per day. Before the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly
- Topical antipruritics: Pramoxine 1%; Doxepin 5% cream
- Topical antibiotics: Clindamycin 1 - 2%; Erythromycin 1% - 2%; Metronidazole 1%; Silver sulphadiazine 1%.
- Oral antibiotics: Doxycycline 100 mg bd; Minocycline 100 mg bd; Oxytetracycline 500 mg bd.

12.1.3.11. Haematotoxicities

Investigational drug at risk: AZD4547 (potentially) olaparib, vemurafenib, and savolitinib

NEUTROPENIA AND LEUKOPENIA

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of study treatment.
Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated GCSF).

PROLONGED HAEMATOLOGICAL TOXICITIES

If a patient develops prolonged haematological toxicity (such as: ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence, neutropenia or thrombocytopenia and/or development of platelet transfusion dependence), weekly differential blood counts including reticulocytes, reticulocyte index and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.
Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to the sponsor. Olaparib treatment should be discontinued if patient's diagnosis of MDS and or AML is confirmed.

12.1.3.12. Peripheral oedema/oedema

Investigational drug at risk: savolitinib, selumetinib, vemurafenib, durvalumab

Treatment interruption may be considered. Diuretic therapy should be considered at the discretion of the investigator. Renal function should be carefully monitored.

12.1.3.13. Potentiation of radiation toxicity

Investigational drug at risk: vemurafenib + cobimetinib

Cases of radiation recall and radiation sensitization have been reported in patients treated with radiation either prior, during, or subsequent to Vemurafenib treatment. Most cases were cutaneous in nature but some cases involving visceral organs had fatal outcomes.
Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment.

12.1.3.14. Malignancies

Investigational drug at risk: olaparib, vemurafenib

Myelodysplastic syndrome/acute myeloid leukaemia

The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5% and the majority of events had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging treatments. The majority of reports were in germline BRCA mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that olaparib should be discontinued and the patient be treated appropriately.

New Primary Malignancies other than MDS/AML

New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents.

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with vemurafenib. It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and be monitored routinely while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per local standard of care. The prescriber should examine the patient monthly during and up to six months after treatment for cuSCC. In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Monitoring should continue for 6 months following discontinuation of Vemurafenib or until initiation of another anti-neoplastic therapy. Patients should be instructed to inform their physicians upon the occurrence of any skin changes.

Non-Cutaneous Squamous Cell Carcinoma (non-cuSCC)

Cases of non-cuSCC have been reported in clinical trials where patients received vemurafenib. Patients should undergo a head and neck examination, consisting of at least a visual inspection of oral mucosa and lymph node palpation prior to initiation of treatment and every 3 months during treatment.
In addition, patients should undergo a chest Computerised Tomography (CT) scan, prior to treatment and every 6 months during treatment.
Anal examinations and pelvic examinations (for women) are recommended before and at the end of treatment or when considered clinically indicated. Following discontinuation of vemurafenib, monitoring for non-cuSCC should continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

New primary melanoma

New primary melanomas have been reported in clinical trials with vemurafenib. Cases were managed with excision and patients continued treatment without dose adjustment. Monitoring for skin lesions should occur as outlined above for cutaneous squamous cell carcinoma.

Other malignancies

Based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Carefully consider benefits and risks before administering vemurafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Guidelines for cuSCC and new primary melanoma surveillance and treatment

A complete dermatological history of prior medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions and photochemotherapy for psoriasis) must be collected at baseline.

- A designated dermatologist will perform regular skin exams to monitor for cuSCC, CC, actinic keratosis, keratoacanthoma and second primary melanomas. Any lesion suspected of being a SCC, BCC, actinic keratosis, keratoacanthoma or second primary melanoma should be appropriately mapped, photographed, with the photos stored digitally and made available to Unicancer upon request.
- Any suspicious lesions (including SCC/KA or other suspicious lesions) identified at baseline and while on study drug must be definitively treated (ie full surgical excision) and sent for pathological examination (shave biopsies are not recommended).
- If the lesion is confirmed to represent one of the aforementioned cutaneous neoplasms, part of the excised tumor tissue will be stored for subsequent biomarker assessment.
- Actinic keratosis, keratoacanthoma or other skin conditions identified by the dermatologist should be treated as per local standard of care.
- Dermatology examinations should occur prior to starting drug, regularly throughout study treatment, and continue for 6 months after last study treatment or until death, withdrawal of consent or lost to follow-up, whichever is earlier.
- In patients who develop cuSCC, it is recommended to continue the treatment without dose adjustment. Dermatology examinations should occur monthly during and up to six months after treatment for cuSCC. Monitoring should continue for 6 months following discontinuation of vemurafenib or until initiation of another anti-neoplastic therapy.

Patients should be instructed to inform their physicians upon the occurrence of any skin changes including rash and photosensitivity. Patients will be referred to a dermatologist for further evaluation as required.

In addition, patients should be advised to avoid sun exposure while on treatment. Sun protective measures are described in section 12.1.3.10.

12.1.3.15. Pancreatitis

Investigational drug at risk: vemurafenib

Pancreatitis has been reported in vemurafenib-treated subjects. Unexplained abdominal pain should be promptly investigated (including measurement of serum amylase and lipase). Patients should be closely monitored when re-starting vemurafenib after an episode of pancreatitis.

12.1.3.16. Immune-mediated reactions

Investigational drugs at risk: durvalumab

INTERSTITIAL LUNG DISEASE / PNEUMONITIS

Immune-mediated pneumonitis is characterized by inflammation focally or diffusely affecting the lung parenchyma that may be result of off-target effects of checkpoint inhibitors against the normal lung parenchyma. (Chow, 2013) Presentations of pneumonitis range from asymptomatic lung infiltrates to a mimic

of severe bacterial pneumonia. For symptomatic patients, complaints and findings may include dyspnea, cough, tachypnea, pleuritic chest pain, and hypoxia.
The frequency of immune-mediated pneumonitis in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 4%. (Topalian et al, 2012; Brahmer et al, 2012).
Because pneumonitis can quickly escalate and become fatal, early recognition is essential. Initial workup includes chest imaging; however, pneumonitis can have highly variable appearances on chest CT scans. In patients with pulmonary metastases or cardiopulmonary comorbidities, evaluation can be particularly challenging as it can be difficult to differentiate between infection, early pulmonary edema, alveolar hemorrhage, immune-mediated pneumonitis, immune-related tumor inflammation, and tumor progression (Topalian et al, 2012). Pneumonitis has also been reported as a complication of cancer treatment associated with lung and breast cancer.
Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Table 13.

ANAPHYLAXIS AND SERIOUS ALLERGIC REACTIONS
As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012).
Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion related reactions are outlined in Table 13.

INFUSION-RELATED REACTIONS
The frequency of Infusion-related reactions in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 10%. A high frequency of mild infusion reactions, was observed with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012).
Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. The typical onset can be within 30 minutes to two hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10 and 30 percent occur during subsequent treatments (Lenz, 2007).

HEPATIC FUNCTION ABNORMALITIES (HEPATOTOXICITY)
Immune-mediated hepatitis/ hepatic toxicity is the inflammation of the liver due to the dysregulation of host immunity related to immune checkpoint inhibitors and often manifests as asymptomatic elevated levels of hepatic transaminases (ALT, AST, bilitubin). In clinical trials, the frequency of immune-mediated hepatitis was typically around ≤1%. (Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013; Tarhini, 2013). In published studies with anti-CTLA-4 mAbs, immune-mediated hepatitis, manifesting as elevations in AST and ALT, has been reported to occur in 3-9% of treated patients (Weber et al, 2012).
In Ipilimumab-treated patients, clinical manifestations of hepatitis included nonspecific symptoms of mild fever, general weakness, fatigue, nausea and/or abdominal pain. In the absence of clinical symptoms, treatment-emergent hepatitis presented asymptomatically as elevated hepatic transaminases. Ultrasonograms of the liver can appear normal or may demonstrate homogenous hepatomegaly, edema, or enlarged perihepatic lymph nodes. Biopsy of the liver most commonly shows a diffuse T-cell infiltrate. Other reported pathology patterns include inflammation focused around either hepatocytes or bile ducts.
If subject presents with liver dysfunction, a high suspicion for irAE hepatitis is warranted, however, it is important to distinguish treatment-related toxicity and rule out other causes of hepatic injury, such as infection, preexisting medical conditions, immunosuppression, metabolic or cardiovascular derangements, other medications, or tumor progression.

RASH/DERMATITIS

Grade 1 and 2 dermatologic toxicities are among the most commonly seen irAEs in patients treated with immune checkpoint inhibitors. Mild dermatitis manifests as a local or diffuse maculopapular rash or erythroderma. Pruritus can accompany the rash or, less commonly, can present as an isolated complaint in the absence of skin findings. Blisters are rarely seen, and their presence signals significant toxicity. Grade 3 to 4 dermatologic irAEs that constitute severe and fatal dermatologic inflammation include Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifestations (Tarhini, 2013; Kaehler, et al 2010).
The frequency of immune-mediated dermatitis (including eczema, eythema, rash maculopapular, rash and pruritus) in clinical trials with immune checkpoint-inhibitors ranged from 1.5% to 33%. (Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013; Tarhini, 2013). Other Life-threatening dermatologic complications such as Steven's Johnson Syndrome or toxic epidermal necrolysis have been seen in fewer than1% of patients. It is important to accurately qualify and quantify cutaneous toxicities.
Pathologic evaluations of biopsy specimens of affected skin often demonstrate eosinophilic infiltration or leukocytoclastic vasculitis; or, they may reveal a lymphocytic predominance characterized by CD8+ T cells, sometimes with tropism for melanin-containing cells. Specifically, in metastatic melanoma patients, the rash associated with immune-checkpoint inhibitors may be indicative of immune response to melanocytes and may progress to vitiligo in some cases. Biopsies showed severe dermatitis with papillary dermal edema, sometimes accompanied by perivascular lymphocytic infiltrate.
Guidelines for the management of subjects with immune-mediated events including dermatitis are outlined in Table 13.

ENTERCOLITIS

Immune-mediated enterocolitis/colitis generally manifests as mild to severe watery diarrhea accompanied by any changes in normal bowel habits or changes from baseline, abdominal pain, nausea/vomiting, or hematochezia. Any grade diarrhea has been the most frequently observed sign/symptom potentially associated with immune-mediated colitis. In severe cases, patients may experience significant dehydration, fever, ileus or peritoneal signs consistent with bowel perforation. Deaths secondary to bowel perforation have occurred.
The frequency of immune-mediated enterocolitis/colitis in clinical trials with immune checkpoint-inhibitors typically ranges from ≤1-8% (Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013; Tarhini, 2013).
Patients with mild symptoms (eg, grade 1 abdominal pain or diarrhea) should be evaluated for infection, including Clostridium difficile infection. Endoscopy performed in these cases may identify an inflamed mucosa with ulceration, which can involve any part of the bowel but most commonly the descending colon (Weber et al, 2012; Wolchock et al, 2010). Tissue biopsies of the colon typically reveal significant inflammatory cell infiltrate.
Guidelines for the management of subjects with immune-mediated events including enterocolitis are outlined in Table 13.

ENDOCRINOPATHY (HYPOTHYROIDISM, HYPERTHYROIDISM, HYPOPITUITARISM)

Immune-mediated endocrinopathies frequently reported in patients treated with checkpoint inhibitors include thyroiditis (hypo- or hyper-), hypopituitarism, hypophysitis, and/or adrenal insufficiency. The frequency of immune-mediated endocrinopathies in clinical trials with immune checkpoint-inhibitors ranged from ≤ 1% to 17%. (Tarhini, 2013; Topalian et al, 2012; Hamid et al, 2013). The most common endocrinopathy seen with ipilimumab is hypophysitis. In clinical trials with other PD-1/PD-L1 inhibitors, endocrine irAEs reported were similar to those reported for ipilimumab, but in contrast, generally milder with fewer events of severe to life-threatening (grades 3–4) irAEs (Sznol and Chen, 2013; Topalian et al, 2012; Wolchok et al, 2013; Hamid et al; 2013)
Clinical presentations of these endocrinopathies include a range of nonspecific symptoms resembling other causes, such as brain metastases or progression of underlying disease. The most common clinical presentation of endocrine irAEs includes nonspecific headache and fatigue, but may also include myalgias, visual field defects, behavioral changes, electrolyte disturbances, loss of appetite and hypotension. (Tarhini, 2013). Patients will generally have abnormal endocrine laboratory test results, that include TSH, free T4, total and free triiodothyronine (T3), cortisol, ACTH, luteinizing hormone, follicle-stimulating hormone, and testosterone (in men).
It is important to note that despite vague symptomatic presentation, there is a risk for serious morbidity or death if the endocrinopathy is not promptly identified and treated
Guidelines for the management of subjects with immune-mediated events including endocrinopathy are outlined in Table 13.

TYPE 1 DIABETES MELLITUS

Type I diabetes mellitus is a heterogeneous disorder characterised by destruction of pancreatic beta cells, culminating in absolute insulin deficiency. The majority of cases are attributable to an autoimmune-mediated destruction of beta cells (type 1a) while a small minority of cases results from an idiopathic destruction or failure of beta cells (type 1b) (Maahs et al 2010). Latent autoimmune diabetes in adults (LADA) is the most common term describing patients with a type 2 diabetic phenotype combined with islet antibodies and slowly progressive betacell failure. Evidence on the occurrence of LADA in relation to adult Type I diabetes mellitus in the general population is usually estimated, due, in part, to limited availability of diagnostic criteria for the LADA (Leslie et al 2006). Across the monotherapy and combination pool of studies there have been no reported events of type 1 diabetes mellitus. However, 1 patient receiving durvalumab monotherapy in an ongoing phase III randomised clinical study outside of the pooled dataset (<0.1%) experienced Grade 3 type 1 diabetes mellitus. The patient, a 60 year old Caucasian male with NSCLC without a history of diabetes mellitus or hyperglycemia, developed severe autoimmune-mediated hyperglycemia (blood glucose 458 mg/dL) 43 days after starting durvalumab, was tested positive for anti-GAD antibody 322 U/mL (reference range 0 to 5 U/mL) and was negative for B-islet antibody. He was diagnosed with type 1 diabetes mellitus by an endocrinologist. The type 1 diabetes mellitus was treated with insulin and resolved with sequelae (insulin dependency). For patients with suspected diabetes mellitus investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin. Guidelines for the management of subjects with immune-mediated events including endocrinopathy are outlined in Table 13.

MYOCARDITIS

A variety of clinical presentations, diagnostic evidence (laboratory, imaging, histopathology), and resulting diagnoses have been described in cases of myocarditis in the literature for other immune checkpoint inhibitors, including heart failure, brady- and tachyarrhythmias, and acute coronary syndrome-like presentations without evidence of ischemia. Treatments are variable, and include immunosuppression and event specific management with agents including beta
blockers, ACE inhibitors, and diuretics. Outcomes can range from rapid response and resolution with immunosuppression to fulminant, fatal events.

Across the durvalumab monotherapy pool of studies, there has been 1 serious report of CTC Grade 3 myocarditis in a 75-year old male patient with pancreatic cancer. Following treatment with corticosteroids the events resolved. This case was confounded by metastases to the myocardium. Subsequent to the DCO, a second serious adverse event of CTC Grade 3 myocarditis, identified by myocardial biopsy (lymphocytic infiltration), was reported in a 78 year-old male with high-grade transitional carcinoma of the bladder with local and hepatic relapses. Cardiac enzymes improved after treatment with high dose corticosteroids and infliximab. Across the durvalumab plus tremelimumab combination pool of studies as of 03 March 2017 there has been one report of myocarditis in a patient with NSCLC. In addition myocarditis has been reported in 3 patients from clinical studies outside of the pooled dataset: 2 patients receiving durvalumab plus tremelimumab and one patient receiving durvalumab plus tremelimumab in combination with cytotoxic chemotherapy agents, etoposide and carboplatin (which resulted in a fatal outcome). Investigators should be aware of such rare, but severe immune-mediated adverse events including myocarditis with its presenting signs/symptoms (.e.g. decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block). For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection) and the appropriate management that includes discontinuing drug (permanently if biopsy-proven immune-mediated myocarditis) and the prompt use of steroids or other immunsosuppressives. Patients with pre-existing cardiac disorders should be closely monitored for deterioration in their cardiac condition, which could suggest new onset myocarditis.

Investigators should exercise clinical judgment in managing actual patients alongside the guidelines presented in the protocol(s). An event that exhibits rapid progression and/or the likelihood for high morbidity/mortality requires that clinical judgment be exercised above and beyond toxicity management guidelines to ensure that treatment is optimally tailored to any given patient's specific case. For example, the general principles outlined in the toxicity management guidelines describe prompt initiation of corticosteroids for both Grade 2 events (that have persisted for 4-5 days) and Grade 3-4 events; clinical judgment applied to this baseline guidance for an event that exhibits rapid progression and/or the likelihood for high morbidity/mortality – such as myocarditis – would warrant prompt initiation of high-dose corticosteroids without delay even for grade 2 cases. Similarly, clinical judgment for patients with suspected myocarditis should lead investigators to obtain a cardiology consult and institute a thorough diagnostic work-up (that includes exclusion of other alternate causes such as infection), and the appropriate management that includes discontinuing drug (permanently if biopsy-proven immune-mediated myocarditis) and, as already noted, the prompt use of steroids or other immunosuppressives.

NEPHRITIS

The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure (Cunard and Kelly 2003). In association to immune-checkpoint inhibitors, two different forms of ipilimumabinduced renal damage are reported, acute kidney injury due to predominant acute granulomatous tubulointerstitial nephritis and nephrotic syndrome in lupus nephritis (Izzedine et al 2014). Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral oedema, haematuria, loss of appetite. As a grouped term, selected renal events including laboratory abnormalities were reported at a frequency of 5.3% (87 patients) across the 1645 patients included in the durvalumab monotherapy pool. Nephritis events were reported at a frequency rate of Uncommon. (5 patients; 0.3%) with 1 CTC Grade 2 autoimmune nephritis, 1 CTC Grade 2 glomerulonephritis, 2 CTC Grade 2 nephritis and 1 CTC Grade 3 tubulointerstitial nephritis. There was 1 CTC Grade 3 nephritis reported in the 560 (0.2%; Uncommon) patients in the durvalumab + tremelimumab combination pool. An additional AESI of acute kidney injury was reported in 26 patients (1.6%) receiving durvalumab monotherapy and 7 patients (1.3%) in the combination pool, 1 of which was CTC Grade 5 in severity; the event was considered not treatment-related by the reporting investigator. Patients should be monitored for changes in renal function (eg, that manifest as elevated serum blood urea nitrogen and creatinine, decreased creatinine CL, electrolyte imbalance, decrease in urine output, or proteinuria and any other findings that may be indicative of nephritis) prior to and periodically during treatment. Prompt treatment with steroids is important as per current established toxicity management guidelines in the study protocols. Guidelines for the management of subjects with immune-mediated events including nephritis or renal dysfunction are outlined in Table 13.

NEUROPATHY/NEUROMUSCULAR EVENTS (TO INCLUDE MG AND GB)

The frequency of immune-mediated neuropathy (including peripheral sensory neuropathy, neuropathy peripheral and peripheral motor neuropathy) in clinical trials with immune checkpoint-inhibitors ranged from ≤1% to 4.5%. (Sznol and Chen, 2013; Topalian et al, 2012; Wolchok et al, 2013; Hamid et al; 2013) Although they are rare, severe neuropathies and myopathies have been observed in patient treated with immune checkpoint inhibitors and include Guillain-Barré syndrome, transverse myelitis, or myasthenia gravis, among other diagnoses.

In the Phase Ib open-label, dose-escalation, and dose-expansion study of durvalumab in combination with, there was 1 medically significant, serious case of myasthenia gravis reported.

Neuropathies associated with ipilimumab have been difficult to assess because these irAEs are transient and present with vague symptoms. Presentations of neurotoxicity may include a mild peripheral sensory neuropathy or muscle weakness. Symptoms of peripheral neuropathy include numbness, tingling, paresthesia (pins and needles sensations), sensitivity to touch, or muscle weakness. In patients with extreme symptoms, they may present with burning pain, muscle wasting, paralysis, or organ dysfunction. Symptoms are typically detected with physical examination findings ranging from sensory changes to loss of deep-tendon reflexes.

Depending on presentation, patients may require neuroimaging, nerve conduction studies, and, potentially, nerve or muscle biopsy to arrive at the diagnosis.

Guidelines for the management of subjects with immune-mediated events including neuropathy or neuromuscular events are outlined in Table 13.

PANCREATITIS

Immune-mediated pancreatitis is an important potential risk. Pancreatitis is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune checkpoint inhibitors. Clinical presentation frequently includes low-grade abdominal pain with accompanying fever and malaise (Weber et al 2012, Di Giacomo et al 2010). Biopsies showed diffuse T-cell infiltrate consistent with immune-mediated pancreatitis (Weber et al 2012). Across the 1645 patients in the monotherapy program, events of pancreatitis were Uncommon to rare. Two patients (0.1%) experienced pancreatitis (CTC Grade 3 and Grade 4 in severity) and 1 patient (<0.1%) with CTC Grade 3 acute pancreatitis. Elevations in amylase and lipase were reported at a frequency rate of Common (0.4% and 0.4%, respectively). In ongoing sponsored studies with durvalumab + tremelimumab therapy in 560 patients, events of pancreatitis were Uncommon; pancreatitis was reported in 4 patients (0.7%) with 3 of these CTC Grade 3 in severity and acute pancreatitis in 1 patient (0.2%). Elevations in amylase and lipase were reported at a frequency of Common (6.1% and 7.0%, respectively). Patients should be monitored for signs and symptoms of pancreatitis including Grade 3 or 4 elevations in lipase and/or amylase. Guidelines for the management of subjects with immune-mediated events including endocrinopathy events are outlined in Table 13.

MYOSITIS/POLYMYOSITIS

The diagnosis of myositis or polymyositis should be suspected in patients who present with proximal muscle weakness and the evaluation should include an examination of the skin, muscle enzyme measurement, antibody testing, any systemic disease manifestations and exclusion of other diseases including drug-induced myopathy. Cases of myositis have been reported with myocarditis in which immune infiltration has been described in skeletal and cardiac muscle (Johnson et al 2016).

In the durvalumab pool of studies as of the DCO, 3 patients (0.2%) reported the event of myositis, including 1 CTCAE Grade 3 in severity. Outside of the pooled dataset, there were 2 fatal events of polymyositis considered as treatment-related by the Investigator. In the durvalumab + tremelimumab combination pool, Grade 3 myositis event were reported in 1 patient (<0.1%). In addition, there were 4 SAEs of myositis reported from studies outside of the pooled dataset. Grade 2 polymyositis was reported in 1 patient (<0.1%) from the combination pooled dataset and 2 additional patients (1 each retrieved from the global safety database and a study outside of the pooled dataset). The severity of these events were Grade 3 and Grade 5 with the latter patient having died due to the event of polymyositis which was considered related by the Investigator. Autopsy showed polymyositis involving the diaphragm and chest wall muscles.

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative aetiologies and initiating prompt treatment with steroids and modification of study drug dose regimen depending on the severity of the event. Refer to the Toxicity Management Guidelines.

12.2. Serious Adverse Events

12.2.1. General definition

A serious adverse event is any untoward medical occurrence, whether or not it is attributable to the study treatment or procedures, that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability / incapacity
- induces a congenital anomaly / birth defect or abortion,
- is medically relevant.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above (e.g: overdose, second cancer, … are considered as medically relevant).

The terms disability and incapacity correspond to any clinically relevant physical or psychic handicap, transient or permanent, with impacts on the physical condition/activity and/or the quality of life of the patient.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

The following events are not considered serious adverse events:

- Hospitalisation < 24 hours*****,
- Hospitalisation already scheduled before the start of the trial and/or which is part of the protocol (biopsy, chemotherapy, etc),
- Hospitalization occurring in the context of tumor progression,
- Progression of disease under study,
- Clinical events related to progression of disease under study are not to be reported as SAEs,
- Death related to progression of disease under study, unless death occurred within 30 days after the last administration of study treatment.

****Hospitalizations < 24 hours for care, procedures, tests or all investigations performed on an outpatient basis without any seriousness criteria associated.***

12.2.2. Study specific definitions

The following events will be considered as medically relevant and must be reported as a serious adverse event (SAEs):

- Drug induced liver injury defined as
  - Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined in section 12.1.3.7 in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.
- Any sign or symptom of at least a grade 3 pneumonitis, with radiographic changes and requiring oxygen support (see the NCI-CTCAE classification for pneumonitis).
- MEDI4736 adverse events of special interest : serious or non serious AE related to immune-mediated reactions such as enterocolitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neuropathy and pneumonitis.

12.2.3. Definition of suspected unexpected serious adverse event (SUSAR)

A serious adverse reaction, the nature or the severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of products characteristics for an approved product).When the outcome of the serious adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

The reference document to assess expectedness for the different study drugs is:

- The Investigator's Brochure for vistusertib, AZD4547, AZD5363, AZD8931, Selumetinib, Vandetanib, Olaparib, Savolitinib and durvalumab.
- The summary of product characteristics for Cobimetinib and Vemurafenib

The expectedness assessment is the responsibility of the Sponsor.

12.2.4. Severity criteria

Severity criterion: The criterion for severity (intensity) must not be confused with the seriousness criterion which is the guide for defining the reporting requirements.

The term "severity" is used here to describe the intensity of a specific event.

The severity of events will be estimated according to the extract from the CTC-AE version 4.0 classification (Appendix 11 – Toxicity Criteria (CTCAE)). The severity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

12.2.5. Reporting serious adverse event

The investigator must immediately and no later than 24 hours following knowledge inform the pharmacovigilance department at R&D UNICANCER of :

- only SAE related to biopsy which occurs after the signature of the screening phase consent; severe toxicities related to chemotherapy before the randomized phase should not be declared as SAEs in the protocol

- any SAE, whether or not related to the research, which occurs from the date of signature of the randomized phase consent until 30 days following the last administration of study treatment (targeted treatment or standard maintenance therapy).

Any delayed SAE, i.e. occurring after a period of 30 days, which are considered to be related to the study treatment(s) or to the research (other treatments used, diagnostic procedures and examinations carried out during the research) must be reported without any limitation in terms of deadline.

Abnormal laboratory results should be reported as SAE if they possibly put at risk the patient or they require medical intervention to prevent an outcome corresponding to one of severity criteria.

Second cancer, whether or not related to the research, must be reported to the Pharmacovigilance Department without any limitation in terms of deadline.

Notification must be carried by fax to the Pharmacovigilance Department at R&D UNICANCER by sending the form entitled “notification of a serious adverse event”, located in the investigator file, completed in English as precisely as possible, dated and signed by the investigator:

R&D UNICANCER

Pharmacovigilance Department, France

Fax: +33(0)1 44 23 55 70

e-mail: pv-rd@unicancer.fr

The investigator should also attach to the form “notification of a serious adverse event”, whenever possible:

- A copy of the hospital report or extended hospitalization report,
- A copy of the autopsy report if necessary,
- A copy of all results of additional investigations carried out, including relevant negative results, and enclosing the normal laboratory values,
- Any other document which he believes to be useful and pertinent.

All these documents must be anonymised.

Additional information can be requested (by fax, mail, telephone or visit) by the monitor and/or the pharmacovigilance department of R&D UNICANCER.

The investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilization of the event or until the death of the patient. This can sometimes mean that the follow-up continues after the patient has left the trial.

The investigator shall send additional information to the pharmacovigilance department at R&D UNICANCER using an SAE declaration form (by ticking the Follow-up no X box to specify that it is a follow-up and not an initial report) as soon as he is aware of the event. He shall also submit the last follow-up at the resolution or stabilization of the SAE.

The investigator must keep the documents concerning the suspected serious adverse event in order to supplement the information previously submitted if necessary.

The investigator must respond to requests for additional information from the Pharmacovigilance department at R&D UNICANCER in order to document the initial observation.

PREGNANCY:

The occurrence of pregnancy during a patient's participation in this trial is not considered as an SAE, however any pregnancy in a female subject or in a female partner of a male subject occuring during the treatment period or withins 30 days after last administration of study treatment must be reported in the same timelines as an SAE by FAX, using a Pregnancy Notification Form form to R&D UNICANCER Pharmacovigilance Department.

Any premature termination of the pregnancy will be reported. While pregnancy itself is not considered to be an SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons or spontaneous abortion will be reported as an SAE.
Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the investigator, will be reported to the sponsor.

12.3. Safety Monitoring of the Study

12.3.1. Steering Committee

Unicancer will appoint a Steering Committee (SC) for this study. SC will include:

- PI and co-PI of the study
- Statistician
- Sponsor representatives
- Investigators
- Bio-pathologists
- Molecular biologists
- Bioinformatician
- One independent expert
- One Fondation ARC representative as permanent guest
- Other participants may be invited depending on the issues raised within the SC

The role of the SC is to provide overall supervision of the study and ensure that the trial is conducted in the rigorous standards set out in the Good Clinical practice. In particular, the SC should concentrate on progress of the trial, adherence to the protocol and patient safety. The SC will as well consider new information relevant to the trial (e.g, reports from IDMC, results of other studies or emergent biomarkers or molecular targets) and should recommend appropriate action such as changes in the trial protocol, additional patient information, stopping or extending the study.

The trial translational research program is under the supervision of the SC which role is to consider how the planned projects should be modified in their objectives or in the techniques they use, or even if they are still relevant in regards to the current state of scientific knowledge. New translational projects proposal will also be evaluated by the SC for implementation.
SC's role is also to identify IDMC members and to call for additional IDMC advice if deemed necessary.

12.3.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be assembled at the beginning of this study to warrant external objective and independent medical and/or statistical review, in order to protect the ethical and safety interests of subjects, and the scientific validity of the study. Members of the IDMC will assess the safety of the interventions during the trial, and monitor the overall conduct of the clinical trial.

If necessary, they could be asked to provide advice or recommendations to the Steering Committee if there are concerns about the safety of one or more of the treatment subgroups, evidence that for any reason trial could fail to conclude or difficulties in accrual that could jeorpardize the validity of the study.

The IDMC will meet before the trial starts, to discuss the protocol, the trial, analysis plan, and future meetings. The frequency of meetings will be every 3 months until the 150th patient has been randomized in the targeted substudy (considering both studies SAFIR02 Lung and Breast). Afterwards, the meetings frequency has been set up to twice a year by the IDMC members. A safety interim analysis is planned after the 60 first randomized patients.

IDMC members will be chosen independent from investigators, funders, sponsor and from any institution involved.

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1. General policy

In order to guaranty the authenticity and accuracy of the data in accordance with the Good Clinical Practices, the sponsor will set up an assurance quality program that includes:

- management of the trial according to the UNICANCER specific operating procedures,
- quality control of the data generated by the investigational site is performed by the study monitor whose role is to match and check the consistency of the data reported in the Case Report Form with respect to the source-documents,
- possible audit of investigational sites,
- possible audit of the pharmacy for control of investigational drug storage conditions, traceability and adequate patient delivery conditions according to the protocole requirements
- centralized review of selected criteria of the protocol.

13.2. Radiological review

An independent radiological review may be scheduled at the end of the trial for the responsive patients. The review committee will be responsible for the validation of responses
Therefore, a systematic DICOM format record must be saved on a CD for each baseline and subsequent radiological tumoral assessment (CT scan or MRI or other method) for all the patients randomized in the study.

14. DATA PROTECTION AND CONFIDENTIALITY MANAGEMENT

Until the trial results are published, the investigator is responsible for insuring the confidentiality of the totality of the information, handled by herself/himself and all other individuals involved in the course of the trial, that are supplied by UNICANCER. This obligation holds neither for the information that the investigator may communicate to the patients within the context of the trial nor for the already published information.
The investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information related to the trial.

Nevertheless, in conformity with the article R 5121-13 of the Public Health Code, both the center and the investigator may communicate information relative to the trial:
- to the Health Minister,
- to the public health inspectors,
- to the ANSM General Director and inspectors.

The trial will not be the subject of any written note and/or oral comment without the prior agreement of the sponsor; the totality of the information that is communicated or obtained during the course of the trial belongs in full right to UNICANCER who can freely use it.

15. DATA REVIEW AND DATA MANAGEMENT

15.1. On-site monitoring

During the study, quality control visits will be performed on active recruiting sites by Unicancer to check:

- the compliance with the protocole requirements and the Good Clinical Practices
- the accuracy of data entered on the CRFs compared to the source documents.
- the compliance with pharmacovigilance reporting requirements

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, radiological assessments, and reports of any other tests or assessments. All information on CRFs must be traceable in the source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

15.2. Database management and quality control

Data from the e-CRFs are registered into the Unicancer database located at Montpellier, centre Val d'Aurelle, under their specific standard operating procedures. Data managers review the completed e-CRFs for completeness and accuracy and generate queries on electronic Data Correction Forms (e-DCF). An identified and validated list of obvious errors can be directly corrected by data managers. e-DCFs are displayed on the e-CRF for completion and electronic signature from the investigational site. Once a CRF is complete, closed for follow-up and all DCF resolved, Unicancer will generate and forward an electronic copy (PDF format) to the investigator. This copy should be printed and signed by the investigator for archiving on site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

When the database will be declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the study statistician and Unicancer.

16. PUBLICATION OF RESULTS

All information resulting from this trial is considered to be confidential, at least until first communication and after appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

Any subsequent publication, abstract or presentation comprising results from the trial must be submitted for examination and approval to the Sponsor.

Furthermore, any written communication or presentation must imperatively include a section that mentions UNICANCER and any institution, investigator, cooperating or collaborating group and scientific society that has contributed to the trial as well as any organism that has financially supported this research.

For the main publication, the first author and writer of the publication will be the principal investigator. She/he may however designate another person to (co-) write the publication.

The other investigators or contributors will appear in the list of co-authors in decreasing order, according to the number of recruited patients or the importance of their contribution (e;g : pathologists, biologists, bioinformatician) regardless of the importance of the cooperating group they belong to, followed by a person representing each cooperating group among the investigation centers that have the highest rates of recruitment. The statistician and a sponsor representative are co- authors as well. The statistician's position is among the first three or the last position of the publication.

In an equal manner, publication of the sub-studies (e.g biological studies) will make mention of the name of the person who has carried out the sub-studies as well as the names of all the individuals who have taken part in carrying out these sub-studies and a sponsor representative.

Inclusion in subsequent publications of representatives of sites with a lower accrual in the list of co-authors will be taken into account.

Any conflict regarding author's name appearance will be submitted to the trial Steering Committee and secondarily to the CSR (Comité Stratégique Recherche) decision in case of major disagreement.

17. ANCILLARY STUDIES

17.1. Circulating tumor DNA analysis (optional for patients)

The utility of measuring circulating acid nucleic for biomarker applications has only recently begun to be explored in the management of solid malignancies (Scaltriti et al, 2007). Through recent advances in genomic technologies it is now possible to characterise specific genomic alterations in a patient's tumor and design personalised assays based on these alterations to measure levels of circulating tumor specific DNA (ctDNA) in the bloodstream. The use of ctDNA for clinical applications has several advantages; ctDNA can be studied from a simple blood test that is easy to perform, safe, minimally invasive and can be repeated frequently during patient follow-up. Following ctDNA levels during cancer therapy presents a unique opportunity for personalised disease monitoring and can provide specific information relating to tumor parameters, treatment responses and mechanisms of drug resistance (Wood et al, 2007; Schwarzenbach et al, 2011; Diaz et al, 2012; Diehl et al, 2008; Leary et al., 2010).

In parallel to the molecular analysis of tumor tissue and after specific informed consent is signed, serial plasma will be collected for ctDNA analysis to allow specific genomic alterations to be followed in real-time to monitor responses and investigate molecular mechanisms of resistance.

Primary Objectives

- To correlate ctDNA mutational profiles with those identified through molecular analysis of tumor material
- To use ctDNA to follow the emergence of molecular alterations possibly linked to resistance to targeted agents

Sample Collection

Whole blood samples will be collected from individuals at selected time-points:

- Baseline: ideally before the initiation of chemotherapy, before cycle 3 at the latest
- After randomization meaning before start of study treatment for all randomized patients, whatever the substudy
- At first disease assessment after randomization (6 weeks after treatment initiation)
- At disease progression

These samples will be collected in all the participating centers

Method

Each blood collection will involve the withdrawal of up to 3x10mL blood into EDTA tubes. Blood collections will be performed at the same time as routine blood tests where possible.

Following blood collection, samples will be processed within 1 hour of collection to retrieve plasma using standard operating procedures provided by the sponsor apart from this study protocol. These samples will then be stored at -80°C for subsequent molecular analysis. Circulating nucleic acids will be isolated using commercial kits, standard protocols or modifications thereof. Molecular characterisation and quantification of ctDNA will be performed using amplification-based (polymerase chain reaction, PCR) techniques and direct plasma sequencing (Forshew et al, 2012).

Molecular characteristics and levels of circulating nucleic acids will be then be compared to clinical characteristics and treatment responses and correlated to findings observed in molecular analysis performed in the metastases. Molecular alterations in ctDNA include mutation detection in 17 genes: TP53, PIK3CA, PTEN, KRAS, BRAF, EGFR, AKT1, AKT2, CASP8, CDH1, CDKN1B, GATA3, MAP2K4, MAP3K1, TBX3, AR and SF3B1. This panel can be modified in order to include additional genes.

17.2. Variation of the molecular profiles of metastases (optional for patients)

This study will be conducted only in centers who will declare their wish to participate. Participation of the patients will also be optional.
Advances in molecular biology and treatment in the last few years have made it possible to gain a better understanding of the genetic mechanism involved in progression of breast cancer and formation of metastases.
Primary breast tumors consist of heterogeneous populations of cells with various genetic changes which determine their ability to metastasize (Fidler at al, 2003; Chiang et al, 2008).

Recent findings suggest that metastatic progression is not strictly regulated by intrinsic genetic modifications in cancer cells, but may also be regulated by the micro-environment of the metastatic site which promotes invasion and angiogenesis. Local factors linked to the tumor environment of the metastatic focus may influence the molecular profiles of the metastases and vary in accordance with the organ being colonized (Kleivi et al, 2007; Varghese et al, 2007).

Although some studies have shown that the genomic anomalies of metastatic tumors were similar to those of the primary lesion, other studies have shown important differences in genetic and protein expression between the primary tumor and its metastases. For example, Bissig and al. have shown that 30% of kidney metastases had a completely different genetic profile from the primary tumor which came from the same patient (Bissig et al, 1999). In NSCBC (non-small-cell bronchial cancer), the expression of biomarkers like EGFR or ERCC1 was discordant between the primary tumor and the metastases in approximately one third of the 49 analyzed cases (Gomez-Roca et al, 2009). It is interesting to note on this subject that the degree of divergence of the molecular profile between the primary tumor and its metastases varies in accordance with whether they are synchronous or metachronous metastases (Balschun et al, 2011).
Furthermore, a genome study among patients with metastatic breast cancer found that a significant percentage of these metastases showed a clonal divergence from their primary tumor (Kuukasjarvi et al., 1997). It is also suggested that the molecular changes differ according to the colonized organ. For example, mutations frequency of KRAS and PIK3CA significantly vary depending on the metastatic site in patients with colon cancer (Tie et al, 2011).

These variations in the tumor molecular profile from one metastatic site to another in the same patient could have an important impact on therapeutic strategy. Indeed, decision on targeted treatments is often guided by the tumor profile from one biopsy only.

Few studies have been carried out comparing genetic expression at different metastatic sites in the same patient. In the study by Kuukasjarvi et al. (1997) previously mentioned, there were only two patients with a primary tumor sample and two different metastatic sites available. In both cases, some molecular changes found in the primary tumor were also observed in the metastases, suggesting that these anomalies came from a common clone. However, other molecular changes differed between the metastatic sites, suggesting a genetic divergence during tumor progression.
We can therefore make the assumption that some molecular changes are intrinsic, while other genetic anomalies are acquired and vary according to the metastatic site, potentially influenced by the local micro-environment. This question is whether it is the common (intrinsic) anomalies, or the acquired anomalies (which vary from one organ to the other) which should guide the choice of target treatments.

Design and primary objective

For patients eligible for SAFIR02 trial and who have at least two different metastatic sites accessible for a biopsy, a second optional biopsy with a specific informed consent will be proposed to allow a comparison of the molecular profile of different metastatic sites. Between 10 and 30 patients will be included in this sub-group.
Secondary objectives

- To compare the gene expression profiles of the different metastatic sites for the same patient
- To determine whether the 'best targets' are the molecular abberations which are common to both metastatic sites.

17.3. Other ancillary studies

1/ Validation of the functional protein activation and exploration of the sequence of events in the signalling pathways, using FISH and CISH, IHC staining, kinome arrays and RPPA analysis.

2/ Investigation of molecular changes that underlie disease progression and the formation of metastases using whole exome sequencing program on normal cells, primary and metastatic tumor material;

3/ Construction of a virtual cell to develop the optimal algorithm able to identify the driver alterations and then to deliver the optimal choice of therapy.

17.4. Retention of samples and confidentiality

For ancillary studies, collections of samples will be centralized and stored at the the Unicancer biobank:

Centre Léon Berard, Centre de Ressources Biologiques
bâtiment Cheney B RDC -
28 rue Laennec, 69008 Lyon - France

For the analysis of the metastases molecular profiles and the research on ctDNA, samples will be made available in accordance with the recommendations and approval of the steering committee of this trial. The research teams will be identified after a call for tender open to participating site.
Regarding samples confidentiality, tubes labels for the study will indicate the screening patient identification number, a 3 letters code and the sample collection date. Research teams will perform sample analysis disconnected from any identification data.

18. ETHICAL AND REGULATORY ISSUES

The clinical trial must be conducted in accordance with:

- the principles of ethics as stated in the last version in use of the Declaration of Helsinki,

- the Good Clinical Practices defined by the International Conference on Harmonization (ICH–E6, 17/07/96),

- the European directive 2001/20/CE on the conduct of clinical trials,

- Huriet's law (n° 88-1138) of December 20th, 1988, relative to the protection of persons participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9th, 2004,

- the law on 'informatics and freedom' (Informatique et Libertés n° 78-17) of January 6th,1978 modified by the law n° 2004-801 of August 6th, 2004 relative to the protection of persons with regard to the computerized processing of personal data,

- bioethic law n°2011-814 of July 8, 2011.

18.1. Ethics Committee (CPP)

Before starting a biomedical research on human patients, the sponsor must submit its project to the opinion of one of the competent Ethics Committee in the region where the principal investigator is practicing.
A request for opinion on the biomedical research project is addressed to the CPP by the sponsor.

Request of substantial modifications to the study protocol are submitted for the CPP's opinion by the sponsor as well.

18.2. Competent authority

Before carrying out or letting a biomedical research to be carried out on its behalf, the sponsor must file a request to be submitted to the competent authority.

18.3. Information and consent of the participants

Prior to carrying out biomedical research on patients, a free and written informed consent form must be signed by each individual participating in the trial after she/he has been informed by the investigator during a physician-patient consultation and after sufficient time for reflection has been allowed.
Information given to the trial participants must cover all of the elements defined by the public health law of August 9th, 2004 and must be written in a simple and comprehensible patient-appropriate manner. Once the participant is acquainted with the information, she/he must sign all the pages of the information booklet. The original booklet will be kept in the investigator's folder and the duplicate copy will be returned to the participant.
The consent form must be dated and signed by both the participant in research and the investigator. The original document is archived by the investigator; a copy will be returned to the research participant).
The information booklet and informed consent form must be associated within the same document to insure that the whole information is given to the research participant.

18.4. Responsibility of the sponsor

The sponsor of the trial is the natural or moral person that: takes the initiative of conducting biomedical research on human subjects, and is therefore liable for the research management and for ensuring the financial support.
The sponsor must be established within the European Community or have one legal representative in an EU member state.

The main sponsor responsibilities are:

- to subscribe a civil-responsibility insurance,

- to register the trial in the European data base and to obtain an **EudraCT** (European Drug Regulatory Authorities Clinical Trials) identification number,

- to request the opinion of the Committee for the Protection of Persons (CPP) on the initial project and the substantial amendments,

- to file the demand of authorization for the initial project and all substantial amendments with the competent authority,

- to provide information on the trial to the heads of the health care centers, the appropriate investigators and the pharmacists,

- to declare to the competent authorities, i.e. the ANSM and the EMEA (the European pharmacovigilance data bank, Eudravigilance) any suspicion of unexpected serious adverse events (SUSAR) related to any of the treatments used in the trial and communicate the information to the CPP and the investigators of the trial,

- the annual declaration of the security report to the competent authority and the CPP,

- the declaration of the beginning and the end of the trial to the competent authority,

- editing the final report on the trial,

- communicating the information on the trial's results to the competent authority, the CPP and the research participants,

- archiving the trial's essential documents in the sponsor folder for a minimal duration of 15 years after the research is ended.

18.5. Responsibilities of the investigators

The principal investigator of each concerned health care center commits to conducting the clinical trial in compliance with the protocol that has been approved by the CPP and the competent authority.
The investigator must not bring any modification to the protocol without having obtained written authorization of the sponsor and the proposed modifications have been authorized by the CPP and the competent authority.

It is the responsibility of the principal investigator:

- to provide the sponsor with its own curriculum vitae and co-investigators' curriculum vitas,
- to identify the members of its team that participate in the trial and to define their responsibilities,
- to insure patient recruitment after the sponsor has issued its authorization.

It is the responsibility of each investigator:

- to collect the informed consent form, dated and signed personally by each individual research participant before any selection procedure specific to the trial may start,
- to regularly fill in the case report form (CRF) for each patient included in the trial and to allow the clinical research assistant mandated by the sponsor to have direct access to the source-documents in order to validate the data collected in the CRF.
- to date, correct and sign the corrections brought to the CRF for each patient included in the trial,
- to accept regular visits of the study monitor and possibly the auditors mandated by the sponsor or the inspectors of the legal competent authorities.

All documentation relative to the trial (protocol, consent forms, CRF, investigators' folders, etc.) as well as all other original documents (laboratory results, radiographic pictures, reports of physician-patient consultations and clinical examinations, etc.) are confidential material and must be kept in a secured location. The principal investigator will be obliged to preserve the data and a list of patient identifications during a minimal period of 15 years after the study has ended.

18.6. Federation of the Patient Committees for Clinical Research in Cancerology

The dedicated task of the FCPRCC (Federation of the Patient Committees for Clinical Research in Cancerology) is to make a second read of the clinical trial protocols in cancerology. The patient committees' federation is coordinated by the R&D UNICANCER, a department of UNICANCER. It gathers both the patient committees of the LNCC and other health care centers. It commits to rereading the protocol and proposing improvements dealing principally with the quality of the letter of information to the patients, the setting up of a treatment and monitoring plan, suggesting measures aimed at ameliorating the comfort of the patients.

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20. APPENDICES

Appendix 1 – Flow chart

Appendix 1 a – Study Flow Chart: Screening phase

	Biopsy screening assessments				
VISITS	≤ 28 days	≤ 14 Days	INCLUSION	Samples collection	Follow up visit
SCREENING ASSESSMENTS					
Signed Patient Information Sheet / Informed Consent Form	X				
Inclusion / exclusion criteria	X				
Demography					
Cancer history and characteristics / prior therapies	X				
Disease status at inclusion / current cancer treatments		X			
Other relevant medical history	X				
Collection of concomitant treatments (1)		X			
Clinical examinations					
Complete clinical examination & vital signs		X			
ECOG performance status		X			
Signs and symptoms		X			
Weight and height		X			
Biological tests					
Hematology: hemoglobin, differential counts, platelets		X(7 and 8)			
Biochemistry : Na, K, Ca, Mg, P, Fasting Plasma Glucose, CO_2, Cl, urea, creatinine, ASAT, ALAT, ALP, total bilirubin, total protein, albumin		X(7 and 8)			
Coagulation profile: PT/INR, aPTT(2)		X(7 and 8)			
β-HCG pregnancy test for women of reproductive potential or urine test (within 72H) (3)		X			
BIOLOGICAL SAMPLES					
Protocol genomic analysis					
Biopsy on metastatic site (4) or archived frozen biopsy(5)				X	
Optional translational research					
Biopsy on a 2nd metastatic site (specific informed consent form)				X	
Blood sample (30 mL) for ct DNA analysis				X(6)	
FOLLOW UP INFORMATION					
Treatment received and response to the treatments					X(9)
Disease and survival status at 24th months					X

(1) Check the current administration of prohibited medications for the randomized part of the study and start considering substituting them.
(2) only if a biopsy is performed
(3) The results must be reviewed prior to undergoing the biopsy procedure. (only if a biopsy is performed)

(4) or primary tumour when locally advanced disease or stage IV at diagnosis

(5) fresh biopsy collected within the year before inclusion

(6) The blood sample collected for ctDNA analysis must be collected ideally before the initiation of induction chemotherapy, before cycle 3 at the latest.

(7) Only for patients that will performed a biopsy.

(8) Biological tests should be done again before the biopsy if not performed within the 5 days after inclusion authorisation.Rresult should be taken into account before performing the biopsy.

(9) For 24 months

Appendix 1 b – Study Flow Chart: Substudy 1 Randomization phase

	Baseline		RANDOMISATION	Cycle 1			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8** (+/-2)	**D15** (+/-2)	**(D22=)D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Signed Patient information Sheet / Informed Consent Form	X												
Inclusion / exclusion criteria	X												
Drug delivery / return / compliance				X			X	X	X	X			
Baseline conditions													
Record of previous chemotherapy	X												
Other relevant medical events since biopsy		X											
Collection of concomitant treatments *(17,19)*		X		X	X	X	X	X	X	X	X(16)	X(16)	X(16)
SAFETY ASSESSMENTS													
Clinical examinations *(17,19)*													
Complete physical examination & weight		X		X	X	X	X	X	X	X	X	X	X
Vital signs : blood pressure, O_2 sat, heart rate, temperature		X		X	X	X	X	X	X	X	X	X	X
ECOG performance status		X		X	X	X	X	X	X	X			
Collection of toxicities / adverse events / signs and symptoms (1)		X		X	X	X	X	X	X	X	X	X	X
Laboratory examinations *(18)*													
Hematology: hemoglobin, differential counts, platelets(2)		X		X	X	X	X	X	X	X (15)			

Biochemistry : Na, K, Ca, Mg, Fasting Plasma Glucose, HCO_3-, Cl, urea, creatinine, ASAT, ALAT, ALP, total bilirubin, total protein, albumin, P[2] [6]		X [3]		X	X	X	X	X	X	X [15]			

	Baseline		**RANDOMISATION**	**Cycle 1 (21 days)**			**Cycle 2**	**Odd Cycles**	**Even Cycle**	**End of treatment / Discontinuation**	**1st FUP visit (30 days post treatment)**	**2nd FUP visit (60 days post treatment)**	**Post treatment FUP**
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8** (+/-2)	**D15** (+/-2)	**D1 (+/-2)**	**D1** (+/-2)	**D1** (+/-2)				
Laboratory examinations [18]													
Coagulation: PT/INR, PTT		X		X			X	X	X	X [15]			
Urinalysis (dipstick glucose, blood, protein)		X		X			X	X	X	X [15]			
β-HCG pregnancy test for women of reproductive potential or urine test (within 72H)		X											
Paraclinical examinations [18]													
Electrocardiogram triplicate 12-lead [8][9]		X		X			X	X	X	X [15]			
LVEF Echocardiogram or MUGA		X											
Bone scan [4]	X												
Brain MRI or tomography[5]	X												
EFFICACY ASSESSMENTS [17]													
Tumor evaluation													

(RECIST)[13]													
Clinical disease assessment	X						X (+/-7)		X (+/-7)	X[20]	X[20]	X[20]	X[20]
Radiologic assessments [7,10]	X						X (+/-7)		X (+/-7)	X[14,20]	X[20]	X[20]	X[20]
Disease and survival status											X	X	X
BIOLOGICAL SAMPLES [17]													
Blood sample (30 mL) for ctDNA analyses				X[11]			X[11](+/-7)			X[12]			

(1) On going toxicities or adverse event have to be monitored until resolution or returned to baseline level. Adverse events must still be collected in the 30 days after the last investigational drug intake, persistent or late AE at any time. Any late Serious Adverse Drug Reaction (SAE related to the study drug), occurring at any time after the 30-day period must be reported to the R&D UNICANCER Safety Office.
(2) any result outside the normal range or inclusion range will be repeated (prior to the first dose) at the discretion of the investigator. Hypocalcemia, hypokalemia and hypomagnesemia should be corrected prior to any study drug administration
(3) Electrolytes should be obtained ≤ 7 days
(4) in case of known bone metastases or if clinically indicated
(5) in case ok known CNS metastases or if clinically justified
(6) Electrolytes should be assessed and corrected at any time when a grade ≥ 2 QTc prolongation is observed (refer to sections 7.6.2 and 12.1.3.5); **Note that :** In case of suspected Drug Induce Live Injury, ASAT/ALAT and bilirubin should be assessed within the 48h (refer to sections 7.6.2 and 12.1.3.7) for detailed management guidelines);
(7) CT scan or MRI of the chest, abdomen and pelvis should be performed for RECIST assessment. They should be repeated 4 weeks after assessment of a PR or CR as per RECIST guidelines.
(8) Pre-dose at day 1 of each cycle : triplicate12-lead ECG for T-wave surveillance and for intervals measurements : QTc, PR, QT, RR, QRS complex (digital ECG are recommended to calculate the standard intervals automatically). The same machine and the same correction method for QT should be used for the same patient all along the study If the QTc is prolonged and >480ms (grade 2), 2 consecutive measurements must be collected approximately 10 minutes apart from the first abnormal measurement. Refer to section 9.1.4. for guidelines.
Note that : Patients treated with a study drug at risk for QTc prolongation and for whom the substitution of a current QT interval-prolonging drug is not possible must perform a weekly QTc monitoring including ECG and electrolytes during the first 4 weeks of co-administration, 3-weekly thereafter as per standard schedule if no QTc prolongation has been noted.
For any patient, if treatment is temporarily interrupted for a QTc prolongation event, continuous ECG monitoring will be performed until the QTc value recovers to grade ≤1 and cardiologist advice
When study drug is restarted due to Grade 3 prolongation of the QTc, triplicate ECG surveillance will again be performed on a schedule similar to the one used at the start of the study, as described in the following drug specific sections.
Note that : Patients for whom the substitution of a current QT interval-prolonging drug is not possible must perform a weekly QTc monitoring including ECG and electrolytes during the first 4 weeks of co-administration, 3-weekly thereafter as per standard schedule if no QTc prolongation has been noted. If treatment is temporarily interrupted for a QTc prolongation event, continuous ECG monitoring (3 times a week) will be performed until the QTc value recovers to grade ≤1. When study drug is

restarted due to Grade 3 prolongation of the QTc, triplicate ECG surveillance will again be performed on a schedule similar to the one used at the start of the study, as described in the drug specific sections (9.1.4).

(9) Standard ECG surveillance is performed with a triplicate measurement. Refer to section 9.1.4. for guidelines.

(10) Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated. Any other radiologic assessment is left to the investigator discretion.

(11) FOR ALL THE CENTERS

A 3x10mL blood sample will be collected from all the randomized patients immediately after the randomization procedure (just before the study drug initiation) and at the first disease assessment.

(12) FOR ALL THE CENTERS: Immediately at disease progression, a 3x10mL blood sample will be collected from all randomized patients.

(13) Tumor evaluation should be repeated every 6 weeks. After 6 months from baseline, radiographic disease assessments should be obtained every 9 weeks until progression.

(14) Radiological assessments should not be repeated if they were obtained less than 6 weeks from withdrawal of therapy.

(15) Laboratory examinations should not be repeated if they were obtained less than 2 weeks from withdrawal of therapy, unless clinically indicated (i.e. on going toxicity surveillance).

(16) Collect subsequent anti-cancer therapy.

(17) Mandatory for arm A1 and B1 during the treatment phase, at the end of the treatment and during the follow-up phase.

(18) Mandatory for arm A1 and as per local standard practive for B1 during the treatment phase, at the end of the treatment and during the follow-up phase

(19) Cycle 1 D8 and D15 examinations are not mandatory for B1 arm if not performed in the usual practice

(20) Tumor evaluation has to be continued during the post-treatment period if withdrawal was not related to disease progression and **should be continued and documented until disease progression or initiation of an antineoplastic treatment.**

(21) C1D1 must occurred during the 7 days after the randomization authorization.

Additional Flow Chart specific to vistusertib

	Baseline			Cycle 1 (21 days)			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8**	**D15**	**D1 (+/-2)**	**D1** (+/-2)	**D1** (+/-2)				
Clinical examinations													
Heart rate and Blood pressure[1]				X (6-8h)									
Monitoring of pulmonary symptoms					X	X	X	X	X	X			
Laboratory examinations													
Thyroïd function tests : TSH, T4, T3[2]		X											
Fasting lipids profile: triglycerides, HDL, LDL, cholesterol[2]		X											
Glycosylated haemoglobin (HbA1C)		X											
Cardiac markers: creatinine kinase, CK-MB, troponins I and T[2]		X											
Urinalysis: Na, K, Urea, creatinine.		X		X[1] (6-8h)						X			
Coagulation: PT/INR, PTT				X[1] (6-8h)									
Hematology: hemoglobin, differential counts, platelets				X[1] (6-8h)									
Insulin				X									

RANDOMISATION

				(0;6-8h)								
Biochemistry : Na, K, Ca, Mg, P, HCO_3-, Cl, serum glucose, urea, creatinine				X(1) (6-8h)								
Paraclinical examinations												
Electrocardiogram triplicate 12-lead (1)				X(1) (6-8h)								

(1) should be performed at pre-dose as described in the flow chart substudy 1 randomisation phase and 6-8 h after the first dose and if clinically indicated thereafter.

(2) should be repeated at any time if clinically indicated

Note that: in case of vistusertib specific toxicities, refer to Table 5 : Vistusertib management guidelines and dose modifications for detailed monitoring guidelines.

Additional Flow Chart specific to AZD5363

	Baseline		RANDOMISATION	**Cycle 1 (21 days)**						**Cycle 2**	**Cycle 3**	**Odd Cycle**	**Even Cycle**	**End of treatment / Discont i-nuation**	**1st FUP visit (30 days post treatment)**	**2nd FUP visit (60 days post treatment)**	**Post treatment FUP**
VISITS	≤ 28 days	≤ 14 days		7days		7days		7days		21 days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D4**	**D8**	**D12**	**D15**	**D19**	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Clinical examinations											(+/-2)						
Heart rate and Blood pressure(1)				X (2h)						X (2h)	X (2h)						
Laboratory examinations																	
Fasting lipids profile: triglycerides, HDL, LDL, cholesterol		X(2)											X(2)	X			
Glycosylated haemoglobin (HbA1C)		X										X(4)		X			
Insulin and Insuline C-peptide		X		X	X					X	X	X	X	X			
Troponins I and T		X				X		X		X	X	X	X	X			
Thyroïd function tests : TSH, T4, T3				X		X		X		X	X	X	X	X			
Biochemistry: Na, K, Ca, Mg, HCO3-, Cl, P, urea, creatinine(1)				X (2h)						X (2h)(5)	X (2h)(5)						
FSH, oestrogen (female only) Testosterone (male only)				X		X		X		X	X	X	X	X			
Urinalysis dipstick: proteinuria						X		X									

Urinary dipstick glucose (3)					X	X	X	X	X								
Random blood glucose (non fasting) (1)				X (0, 2h)						X (0, 2h)	X (0, 2h)	X (0, 2h)	X (0, 2h)				
Paraclinical examinations																	
Electrocardiogram (12-lead ECG) (1)				X (2h)						X (2h)							
LVEF Echocardiogram or MUGA(3)										X (+/-7)							

(1) should be performed at pre-dose and 2 h after the first dose of the cycle 1
(2) at baseline and every 4 cycles
(3) at day 1 cycle 2 and thereafter only if clinically indicated The same method as baseline should be used (+/- 7 days).
(4) pre-dose at cycle 5 and then every 12 weeks
(5) Patients taking AZD5363 and metformin in combination should have creatinine assessments conducted as part of the routine clinical chemistry with additional monitoring of creatinine at the discretion of the investigator.
Note that : in case of AZD5363 specific toxicities, refer to Table 7 : AZD5363 management guidelines and dose modifications for detailed monitoring guidelines.

Additional Flow Chart specific to AZD4547

	Baseline		RANDOMISATION	Cycle 1 (21 days)			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 Days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8**	**D15**	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Laboratory examinations													
Troponins I and T		X					X	X	X	X			
Calcium x Phosphate product		X		X			X	X	X	X			
Paraclinical examinations													
Ophthalmologic exam (1)	X						X(2) (+/-14)	X(2) (+/-14)					
OCT scan	X						X(3) (+/-14)	X(3) (+/-14)					
LVEF Echocardiogram or MUGA (4)							X (+/-7)		X (+/-7)	X			

(1) Ophthalmic assessments should be performed by an ophthalmologist or licensed practitioner and include in the order stated: visual acuity, Amsler grid, Schirmer's test, slit lamp examination, fundoscopy and lens examination.
(2) should be performed once per cycle for the first 3 cycles and every 2 cycles thereafter
(3) should be performed once per cycle for the first 3 cycles and on the occurrence of clinical symptoms or signs suggestive of RPED thereafter
(4) should be performed at day 1 cycle 2 and every 4 cycles thereafter and if clinically indicated thereafter. The same method as baseline should be used (+/- 7 days).

Note that: in case of AZD4547 specific toxicities, refer to Table 6 : AZD4547 management guidelines and dose modifications for detailed monitoring guidelines

Additional Flow Chart specific to AZD8931

	Baseline		RANDOMISATION	Cycle 1 (21 days)			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8**	**D15**	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Clinical examinations													
Monitoring of pulmonary symptoms					X	X	X	X	X	X			
Paraclinical examinations													
Ophthalmologic exam [(1)]	X												
Electrocardiogram (triplicate 12-lead ECG) [(3)]				X (0,6h)[(3)]									
Echocardiogram or MUGA [(2)]									X[(2)](+/-7)	X			

(1) Ophthalmic assessments should be performed by an ophthalmologist or licensed practitioner and include in the order stated: visual acuity, Amsler grid, Schirmer's test, slit lamp examination, fundoscopy and lens examination.
Should be performed at baseline and thereafter only if an AE of visual disturbance occurs
(2) should be performed every 4 cycles starting C4D1 and if clinically indicated thereafter. The same method as baseline should be used (+/- 7 days).
(3) should be performed at pre-dose and 6h after the first dose of the cycle

Note that: **in case of AZD8931 specific toxicities, refer to table 8 for detailed monitoring guidelines.**

Additional Flow Chart specific to vandetanib

	Baseline		RANDOMISATION	Cycle 1 (21 days)			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8**	**D15**	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Clinical examinations													
Monitoring of pulmonary symptoms					X	X	X	X	X	X			
Paraclinical examinations													
Electrocardiogram (triplicate12-lead ECG) (1)				X (6h)	X								
Laboratory examinations													
Thyroïd function tests : TSH, T4, T3(2)		X											

(1) should be performed at pre-dose as described in the flow chart substudy 1 randomisation phase and 6 h after the first dose of the cycle

(2) only in patients receiving concomitant thyroid hormone replacement.

Note that : in case of vandetanib specific toxicities, refer to Table 10 : Vandetanib management guidelines and dose modifications for detailed monitoring guidelines.

Additional Flow Chart specific to selumetinib

	Baseline			Cycle 1 (21 days)			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 days	≤ 14 Days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS			RANDOMISATION	**D1**	**D8**	**D15**	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Clinical examinations													
Monitoring of pulmonary symptoms					X	X	X	X	X	X			
Monitoring of muscle weakness [2]					X	X	X	X	X	X			
Laboratory examinations													
Calcium x Phosphate product				X	X	X	X	X	X	X			
Creatinine kinase[3]		X				X[3]		X[3]					
Paraclinical examinations													
Ophthalmologic exam [1]	X												

(1) Ophthalmic assessments should be performed by an ophthalmologist or licensed practitioner and include in the order stated: visual acuity, Amsler grid, Schirmer's test, slit lamp examination, fundoscopy and lens examination.

Should be performed at baseline and thereafter only if an AE of visual disturbance occurs (including OCT scans). Refer to Figure 8 for selumetinib management of visual toxicity.

(2) if it occurs and it cannot be explained, the cause should be ascertained using local diagnostic algorithms.

(3) Creatine kinase will be monitored at cycle 1 D15 and at D1 of each odd cycle and as clinically indicated (especially if doubling in value compared to last result of if muscle symptoms).

Note that: in case of selumetinib specific toxicities, refer to Table 9 for detailed monitoring guidelines.

Additional Flow Chart specific to olaparib

	Baseline		**RANDOMISATION**	**Cycle 1 (21 days)**			**Cycle 2**	**Odd Cycles**	**Even Cycle**	**End of treatment / Discontinuation**	**1st FUP visit (30 days post treatment)**	**2nd FUP visit (60 days post treatment)**	**Post treatment FUP**
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8**	**D15**	**D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Clinical examinations													
Hematology: reticulocytes, reticulocyte index and peripheral blood smear (1)					X(1)	X(1)	X(1)	X(1)	X(1)	X(1)			

(1) weekly in case of prolonged haematological toxicity.

Note that: in case of olaparib specific toxicities, refer to Table 11 : Olaparib management guidelines and dose modifications for detailed monitoring guidelines.

Additional Flow Chart specific to savolitinib

	Baseline			**Cycle 1**			**Cycle 2**	**Odd Cycles**	**Even Cycle**	**End of treatment / Discontinuation**	**1st FUP visit (30 days post treatment)**	**2nd FUP visit (60 days post treatment)**	**Post treatment FUP**
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	21 days	21 days	21 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8** (+/-2)	**D15** (+/-2)	**D22=D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Paraclinical examinations													
LVEF Echocardiogram or MUGA									X(1) (+/-7)				
Laboratory examinations													
ASAT, ALAT, ALP, total bilirubin,			RANDOMISATION	X(4)	X(4)	X(4)	X(4)						
Thyroïd function tests : TSH, T4, T3		X							X(1)	X			
Creatine kinase									X(2)	X(2)			
Urine dipstick and/or microscopy									X(3)	X(3)			

(1) should be performed every 4 cycles until end of treatment and if clinically indicated thereafter. For LVEF, the same method as baseline should be used.
(2) should be performed as clinically indicated in case of fatigue.
(3) should be performed as clinically as clinically indicated in case of renal disorders.
(4) should be done weekly during the first 9 weeks of treatment
Note that: in case of savolitinib specific toxicities, refer to Table 12 : Savolitinib management guidelines and dose modifications for detailed monitoring guidelines.

Additional Flow Chart specific to vemurafenib and cobimetinib

	Baseline		RANDOMISATION	Cycle 1			Cycle 2	Odd Cycles	Even Cycle	End of treatment / Discontinuation	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
VISITS	≤ 28 days	≤ 14 days		7days	7days	7days	28 days	28 days	28 days	Within the week of withdrawal			Every 3 months for 2 years
TREATMENTS				**D1**	**D8** (+/-2)	**D15** (+/-2)	**D22=D1** (+/-2)	**D1** (+/-2)	**D1** (+/-2)				
Baseline conditions													
A complete history of or ongoing retinal disease	X												
A complete dermatological history of prior medications and cuSCC risk factors	X												
Clinical examinations													
Dermatology evaluation by a dermatologist for cuSCC, basal cell carcinoma (BCC), actinic keratosis, keratoacanthoma [(1)] Evaluation of non-cuSCC : Anal and Head and Neck examination	X						X[(1)]		X[(1)]	X[(2)]			X[(3)]
Skin, anal, head and neck examination [(4)]	X					X	X	X	X	X	X	X	X[(4)]
Evaluation of non-cuSCC : gynecologic examination [(5)]	X								X[(5)]	X[(5)]			

Monitoring of pulmonary and visual symptoms					X	X	X	X	X	X			
Ophthalmic examination									X(6)	X(6)			
Paraclinical examinations													
Evaluation of non-cuSCC : Chest CT Scan (7)	X								X(7)				X(7)
LVEF Echocardiogram or MUGA							X(8)		X(8)	X			

(1) Dermatology evaluation by a dermatologist 28 days (+/- 8 days) after starting vemurafenib and every 12 weeks thereafter until drug discontinuation, for cuSCC, basal cell carcinoma (BCC), actinic keratosis, keratoacanthoma and second primary melanomas. Anal and Head and Neck examination (as part of the evaluation for non-cutaneous SCC) performed by the dermatologist will consist of at least a visual inspection of oral mucosa and lymph node palpation. In patients who develop cuSCC, dermatology examinations should occur monthly during and up to six months after treatment for cuSCC.

(2) If not done within the last 12 weeks except when suspected lesions.

(3) Dermatology evaluation by a dermatologist at months 3 and 6 after last study treatment.

(4) As part of the complete clinical examination performed at each visit, the treating physician will also maintain a regular screening as part of the evaluation for cutaneous and non-cutaneous SCC. Examination will consist of at least a visual inspection of skin, anal margin, oral mucosa and lymph node palpation. Screening will be maintained for a maximum of 6 months after treatment discontinuation.

(5) Gynecologic examination is recommended before and at the end of treatment or when considered clinically indicated. The baseline pelvic examination for women must be done within 6 months before the treatment.

(6) Should be performed only if an AE of visual disturbance occurs, and as clinically indicated. Ophthalmic assessments should be performed by an ophthalmologist or licensed practitioner and include in the order stated: visual acuity, Amsler grid, Schirmer's test, slit lamp examination, fundoscopy and lens examination.

(7) Chest CT scan prior to treatment, every 6 months during treatment and at 6 months after treatment discontinuation (possibility of using the tumor assessment CT scan).

(8) Should be performed after the first month of treatment and at least every 2 months or as clinically indicated until treatment discontinuation. All patients restarting treatment with a dose reduction of cobimetinib after the management of a LVEF decrease should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then as clinically indicated.

Note that: in case of vemurafenig or cobimetinib specific toxicities, refer to Table 13 : Vemurafenib management guidelines and dose modifications and Table 14 : cobimetinib management guidelines and dose modificationsfor detailed monitoring guidelines.

Appendix 1 c – Study Flow Chart: Substudy 2 Randomization phase

	Baseline		RANDOMISATION	Every 2 weeks	Every 4 weeks	Every 6 weeks	1st FUP visit (30 days post treatment)	2nd FUP visit (60 days post treatment)	Post treatment FUP
WEEK	≤ 28 days	≤ 14 days		0[21] ,2,4,6,8, etc	0, 4,8,12,16, etc (+/-2)	0, 6,12,18,24, etc (+/-2)	(+/-7)	(+/-7)	Every 3 months for 2 years
Signed Patient information Sheet / Informed Consent Form	X								
Inclusion / exclusion criteria	X								
durvalumab administration				D1					
Baseline conditions [18]									
Record of previous chemotherapy	X								
Other relevant medical events since biopsy		X							
Collection of concomitant treatments		X		D1			X[17]	X [17]	X (+/-7)[17]
SAFETY ASSESSMENTS									
Clinical examinations [18]									
Complete physical examination & weight		X			D1		X	X	X (+/-7)
Vital signs [1](pre, during and post-infusion assessment) : blood pressure, O_2 sat, heart rate, temperature		X		D1			X		
ECOG performance status		X			D1		X	X	At 3 months
Collection of toxicities / adverse events / signs and symptoms [2]		X		D1			X	X	X (+/-7)
Laboratory examinations [19]									
Hematology: hemoglobin, differential counts, platelets[3]		X			D1		X	X	At 3,12 months
Liver enzyme panel : ASAT, ALAT, ALP, GGT, total bilirubin[4]		X		D1			X	X	At 3 months

Biochemistry : Na, K, Ca, Mg, glucose, HCO_3-, Cl, urea, creatinine, total protein, albumin, amylase, lipase, LDH, uric acid[3]		X [3]			D1		X	X	At 3 months
Thyroid function tests : TSH, fT3, fT4[5]		X			D1		X		
Coagulation: PT/INR, PTT		X							
Urinalysis : bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance [6]		X			D1				
Hepatitis B and C; HIV		X							
β-HCG pregnancy test for women of reproductive potential or urine test (within 72H)		X							
Paraclinical examinations [19]									
Electrocardiogram triplicate 12-lead [7]		X		Week 0 only D1 (0,3h)[8]					
Bone scan [9]	X								
Brain MRI or tomography[10]	X								
EFFICACY ASSESSMENTS [18]									
Tumor evaluation (RECIST)[20]									
Clinical disease assessment	X					D14 (+/-7)[13]	X[13]	X[13]	X[13]
Radiologic assessments [11,12]	X					D14 (+/-7)[13,14]	X[13]	X[13]	X[13]
Disease and survival status							X	X	X
BIOLOGICAL SAMPLES [18]									
Blood sample (30 mL) for ctDNA analyses				X[15]		X[15]	X[16]		

(1)

Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

(2) On going toxicities or adverse event have to be monitored until resolution or returned to baseline level. Adverse events must still be collected in the 30 days after the last investigational drug administration, persistent or late AE at any time. Any late Serious Adverse Drug Reaction (SAE related to the study drug), occurring at any time after the 30-day period must be reported to the R&D UNICANCER Safety Office.

(3) If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion.

Any result outside the normal range or inclusion range will be repeated (prior to the first dose) at the discretion of the investigator.

(4) If total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

(5) Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system

(6) Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

(7) Standard ECG surveillance is performed with a triplicate measurement. Refer to section 9.1.4 for guidelines.

(8) On Day 1, ECGs will be recorded within an hour prior to start of durvalumab infusion and at least one time point 0 to 3 hours after the infusion and as clinically indicated.

(9) In case of known bone metastases or if clinically indicated

(10) In case ok known CNS metastases or if clinically justified

(11) CT scan or MRI of the chest, abdomen and pelvis should be performed for RECIST assessment. They should be repeated 4 weeks after assessment of a PR or CR as per RECIST guidelines.

(12) Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated. Any other radiologic assessment is left to the investigator discretion.

(13) Tumor evaluation has to be continued during the post-treatment period if withdrawal was not related to disease progression (i.e toxicity or protocolar end of durvalumab after 26 doses max) and **should be continued and documented every 6 weeks until disease progression or initiation of an antineoplastic treatment.**

(14) Radiological assessments should not be repeated if they were obtained less than 6 weeks from withdrawal of therapy

(15) FOR ALL THE CENTERS

A 3x10mL blood sample will be collected from all the randomized patients immediately after the randomization procedure (just before the study drug initiation) and at the first disease assessment.

(16) FOR ALL THE CENTERS: Immediately at disease progression, a 3x10mL blood sample will be collected from all randomized patients.

(17) collect subsequent anti-cancer therapy

(18) Mandatory for arm A2 and B2 during the treatment phase, at the end of treatment and during follow-up phase.

(19) Mandatory for arm A1 and as per local standard practive for B1 during the treatment phase, at the end of treatment and during the follow-up phase.

(20) Tumor evaluation should be repeated every 6 weeks. After 6 months from baseline, radiographic disease assessments could be obtained every 9 weeks until progression.

(21) C1D1 must occurred during the 7 days after the randomization authorization.

Note that: in case of durvalumab specific toxicities, refer to
Table 15 : Durvalumab management guidelines and dose modifications for detailed monitoring guidelines

Appendix 2 – Freezing procedure

Freezing procedure, quality control and sample circuit is available on the podcast:

http://bit.ly/safir02-circuit-echantillons

Alternative freezing procedure is outlined below :

The biopsy will be performed according to local procedures. The biopsy product will be frozen immediately whenever possible, but no later than 30 minutes after the procedure.

The patient ID will be written on the labels provided specifically for the study. The labels will be affixed to the tube before freezing.

The following procedure will be used for preserving specimens in the OCT compound:

Each specimen will be placed in the bottom of a tube (Versandtube® 18x42, Semadeni ref 2640). Close the tube and add Tissue-Tek (OCT compound™ Tissue-tek Bayer ref 22007-1) to the tube (1/3 full).

Place a beaker full of methyl butane (Methyl-2-Butane spectroscopy Uvasol 1 ref 18292-1) in liquid nitrogen. Put the tube in the beaker when bubbles appear in the methyl butane. The nitrogen must not come into contact with the tube until the Tissue-Tek has solidified.

Once the Tissue-Tek has solidified, place the tube in the liquid nitrogen or cool to -80°C.

Appendix 3 – Procedure for samples fixation

The purpose of this appendix is to describe the ideal procedure for fixing tissue samples for future biopathological studies. This appendix applies to the tissue samples left over after at least one fragment has been cryopreserved in nitrogen or in OCT medium for the CGH technique.

1. Immerse the biopsy fragments into a flask of formalin buffered to 10% as soon as possible (but no later than 1 hour) after taking the sample.

   This fixative is ideal for fluorescent in situ hybridization (FISH), chromogenic in situ hybridization (CISH), or immunohistochemistry (ICH).

2. The optimum fixation time is between 6 and 36 hours.

3. When several biopsy fragments are collected, it is recommended to embed only one biopsy fragment per block/cassette to avoid running out of tissue material for subsequent analysis.

Appendix 4 – list of selected genes

1/ NGS gene selection *(panel V2.0)*

Gene	Mutation	Comm.
AKT1	HotSpot	p.E17K
AKT2	HotSpot	p.E17Klike
AKT3	HotSpot	p.E17Klike
ALK	HotSpot	ex 20,22,23,24,25
ATM	FullCDS	96,40%
BRAF	HotSpot	Ex 11&15
BRCA1	FullCDS	92,80%
BRCA2	FullCDS	99,10%
CTNNB1	HotSpot	Ex3
DDR2	HotSpot	Ex6,9,14-16,18
EGFR	HotSpot	Ex3,6,7,15,18, 19,20,21
ESR1	HotSpot	Ex4,5,7,8
EZH2	HotSpot	Ex16
GNA11	HotSpot	Ex4,5
GNAQ	HotSpot	Ex4-5
H3F3A	HotSpot	Ex2
HER2 /Erbb2	HotSpot	Ex8, 17-22, 24
HER3/ Erbb3	HotSpot	Ex2,3,6-8
HER4 / Erbb4	HotSpot	Ex1
FBXW7	HotSpot	Ex5,8-11
FGFR1	HotSpot	ex4,7,12,14,15
FGFR2	HotSpot	Ex3,7,9,12,14
FGFR3	HotSpot	Ex7,9 (couv 52%),14,16,18
FGFR4	HotSpot	Ex11,12,14,16
FOXL2	HotSpot	Ex1
GATA3	HotSpot	Ex5
HIST1H3B	HotSpot	Ex2
HRAS	HotSpot	Ex2,3,4
IDH1	HotSpot	Ex4
IDH2	HotSpot	Ex4
INPP4B	HotSpot	Ex13,14,24
JAK2	HotSpot	Ex14
KDR	HotSpot	Ex7,8,23
KEAP1	HotSpot	Ex2,3,4,6
KIT	HotSpot	Ex8 à 14, 17, 18
KRAS	HotSpot	Ex 2,3,4
MAP2K1	HotSpot	Ex3,4,6,7,11
MAP2K2	HotSpot	Ex2,4
MAP2K4	FullCDS	99,30%
MAP3K1	FullCDS	95,40%
MET	HotSpot	Ex14 (+introns), 16,19-21
MTOR	FullCDS	99,10%
nf1	FullCDS	98,50%
NFE2L2	HotSpot	Ex2
NRAS	HotSpot	Ex 2,3,4
PALB2	FullCDS	96,60%
PDGFRA	HotSpot	Ex12,14,15,18
PIK3CA	HotSpot	Ex2,5,8,10,14,21
PIK3R1	HotSpot	Ex9-15
POLE	HotSpot	Ex6,9,11,13, 14,16,19,31, 36
PPP2R1A	HotSpot	Ex5,6
PTEN	FullCDS	88,60%
PTPN11	HotSpot	Ex3,13
RAD51B	FullCDS	94,00%
RAD51C	FullCDS	100%
RAC1	HotSpot	Ex2
RET	HotSpot	Ex10,11,13,15,16
RHOA	HotSpot	Ex2
ROS1	HotSpot	Ex 38
SF3B1	HotSpot	Ex14-19
STK11	FullCDS	94,30%
TP53	FullCDS	97,70%
TSC1	FullCDS	97,90%
TSC2	FullCDS	97,20%
VHL	FullCDS	97,80%

2 / CGH array gene selection (panel V2.0)

Gene	Gene	Gene	Gene	Gene
AKT1	FGFR1	VHL	MYC	RUNX1
AKT2	FGFR2	AR	FGF9	CDH1
PIK3CA	FGFR3	BRCA1	FGF4	GATA3
PTEN	HER2	BRCA2	TOP2A	KIT
PDK1	HER1(EGFR)	ATR	TP53	ROS1
AKT3	HER3	ATM	NOTCH1	ERBB4
INPP4B	KRAS	IGF1R	NOTCH2	PDPK1
PIK3R1	HRAS	IGF1	NOTCH4	KDR
PIK3R2	NRAS	PDGF	PAK1	DDR2
RPTOR	BRAF	PDGFRa	CCND1	FBXW7
TSC1	FRS2	ALK	MAP2K1	CTNNB1
TSC2	MET	MDM2	MAP3K1	APC
STK11 (LKB1)	PIK3CB	ESR1	MAP2K4	CDH1
NF1	RET	PGR	MAP3K13	RB1
MTOR	VEGFA	FGFR4	CBFB	KEAP1
ATM	ESR1	EZH2	GNA11	GNAQ
H3F3A	FOXL2	GATA3	HIST1H3B	IDH1
IDH2	JAK2	MAP2K2	PALB2	POLE
RAD51B	RAD51C	RHOA		

Appendix 5 – List of medications and targets (V6.0 14 March 2017)

Drug	Action	IC_{50}	Currently matched actionable genetic aberrations
AZD5363	AKT1 AKT2 AKT3 PKA ROCK1 ROCK2	< 10 nM < 10 nM < 10 nM < 10 nM 126 nM 56 nM	AKT1 amp / mut AKT2 mut/amp PIK3CA mut PIK3CA amp PTEN inactivation PDPK1 amp AKT3 amp or translations INPP4B inactivation PIK3R1 mut / amp PIK3CB amp
Vistusertib	mTOR (C1 and C2)	2.81 nM	RPTOR amp RICTOR amp TSC1 mut TSC2 mut STK11(LKB1) inactivation MTOR mut IGF1R amp
AZD4547	FGFR1 FGFR2 FGFR3 FGFR4 VEGFR-2 (KDR) MARK3 IGF1R	< 5 nM < 5 nM < 5 nM 165 nM 24 nM 60 nM 581 nM	FGFR1 ampl/ mut FGFR2 ampl / mut FGFR3 ampl/ mut
Selumetinib	MEK	10 to 14 nM	KRAS mut / amp HRAS mut NRAS mut FRS2 amp PTPN11 mut NF1 inactivation
Vandetanib	VEGFR-2 (KDR) EGFR RET	0.04 µM 0.5 µM 0.1 µM	HER1(EGFR) amp / mut RET mut/ amp / translocation VEGFA amp VEGFR-2 (KDR) amp/ mut VHL inactivation
Olaparib	PARP1	5 nM	BRCA1 inactivation BRCA2 inactivation ATM inactivation PALB2 inactivation RAD51B inactivation RAD51C inactivation
Savolitinib	MET	5 nM	MET amp / mut
Vemurafenib + Cobimetinib	BRAF		BRAF amp / mut MAP2K1(MEK1) amp / mut MAP2K2(MEK2) amp / mut

Order of preference for treatment	Genetic abnormality	Therapeutic intervention
1	**MET exon 14 splice site mut**	Savolitinib
2	**MAP2K1 (MEK1) mut**	Vemurafenib + Cobimetinib
	MAP2K2(MEK2) mut	
	BRAF mut	
3	**BRCA1 inactivation**	Olaparib
	BRCA2 inactivation	
	ATM inactivation	
4	***KRAS*** mut (except if *STK11(LKB1) inactivation* is also present)*	Selumetinib
	***BRAF* mut.**	
5	***FGFR1* amplification**	AZD4547
	***FGFR2* mut**	
	***FGFR3* mut**	
7	***PIK3CA* amplification**	**AZD5363** (or vistusertib if the number of pts with this abnormality is high)
	***PIK3CA* mut**	
	***PTEN* inactivation**	
	***AKT1* mut**	AZD5363
8	***RET* translocation (validated by FISH)**	Vandetanib
6	***MET* amplification**	Savolitinib
	METmut other than exon 14 splice site mut	
9	***STK11* (LKB1) inactivation**	Vistusertib
10	**Other**	

*** : when LKB1 /STK11 presents a biallelic inactivation and is associated to an activating mutation of KRAS, selumetinib should not be selected (resistance has been demonstrated in pre-clinical studies;Chen et al., Nature, 2012,483:613-617) and vistusertib preferred.**

Appendix 7 – List of Substrates, inhibitors and inducers of Cytochrome P450

For list of substrates, inhibitors and inducers of CYP P450, refer to the website :
http://medicine.iupui.edu/clinpharm/ddis/main-table/

The **washout period is 14 days** prior to the first dose of study drug, except those for which the minimum wash-out period is longer (Fluoxetine and Phenobarbital: 5 weeks, Rifabutin : 3 weeks and amiodarone: 27 weeks).

Appendix 8 – Drugs at risk of Torsades de Pointes

Source : http://www.crediblemeds.org/healthcare-providers/drug-list/

1 / DRUGS WITH KNOWN RISK OF TORSADES DE POINTES

This list includes drugs that are generally accepted by the www.QTdrugs.org Advisory Board of AZCERT to have a risk of causing torsades de pointes.

2 / DRUGS WITH POSSIBLE RISK OF TORSADES DE POINTES

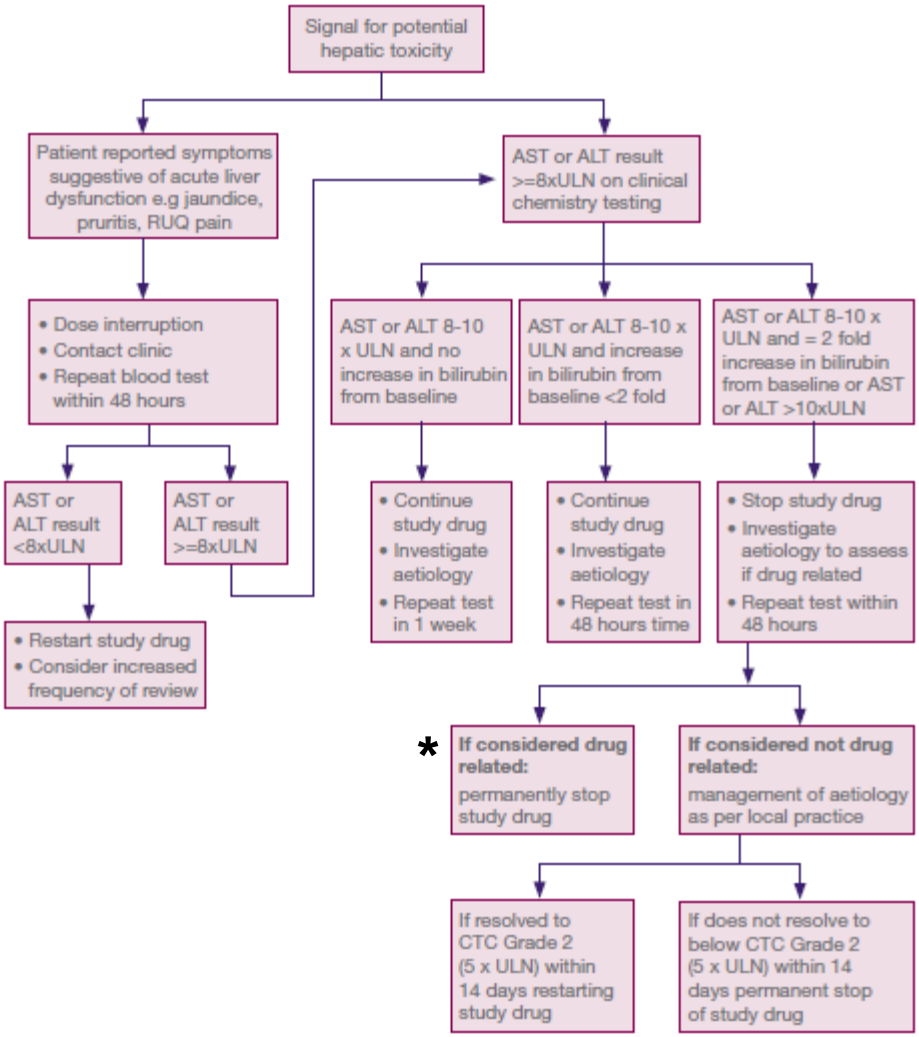
This list includes drugs that prolong the QT interval on the electrocardiogram but at this time lack substantial evidence for being a cause of torsades de pointes.

3 / DRUGS WITH CONDITIONAL RISK OF TORSADES DE POINTES (TdP)

This list includes drugs that carry a risk of TdP and/or excessive QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose or co-administration of interacting drugs. In the absence of these conditions, these drugs have not been reported to cause TdP.

Appendix 9 – Guidance on management of hepatotoxicity

The management algorithm presented here provides guidance on management of patients reported symptoms of potential acute liver dysfunction and of liver transaminase results in excess of 8x upper limit of normal occurring at any time during the study, with any of the study drugs.



* = Drug Induced Liver Injury (DILI)

Appendix 10 – Assessment of general condition- WHO and Karnofsky scores

EVALUATION DE L'ETAT GENERAL EN FONCTION DE LA CLASSIFICATION DE KARNOFSKY

ETAT GENERAL KARNOFSKY	ECHELLE		ETAT GENERAL ECOG-ZUBROD/WHO
Normal, pas de plaintes.	100	0	Activité normale, sans restriction.
Activité normale. Signes ou symptômes mineurs de la maladie. Activité normale avec efforts.	90 80	1	Restreint pour des activités physiques importantes mais patient ambulatoire et capable de fournir un travail léger.
Capable de se prendre en charge, mais incapable d'avoir une activité normale ou de travailler. Nécessite occasionnellement de l'aide, mais capable de subvenir à la plupart de ses besoins.	70 60	2	Ambulatoire et capable de se prendre en charge, mais incapable de fournir un travail pendant plus de 50 % de son temps.
Nécessite aide et soins médicaux fréquents. Nécessite soins médicaux et aide importante.	50 40	3	Capacité de prise en charge propre beaucoup plus limitée. Passe plus de 50 % de son temps au lit ou dans une chaise.
Sévèrement limité, grabataire. Indication d'hospitalisation, quoique la mort ne soit pas imminente. Gravement atteint. Hospitalisation nécessaire. Traitement symptomatique nécessaire.	30 20	4	Complètement grabataire. Incapable de se prendre en charge. Le patient reste totalement couché au lit ou sur une chaise.

Appendix 11 – Toxicity Criteria (CTCAE)

Please refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE)
(Published: June 14, 2010)**, separately joined to this protocol or available on :**

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 12 – Classification RECIST V1.1quick reference
(Eur. J. Cancer, 45(2009), 228-247)

Full article available on: http://ctep.cancer.gov/

"New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)" E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij

French summary:

Lésions à l'inclusion :
Les lésions et les ganglions sont classés individuellement comme étant mesurable ou non mesurable.

Maladie mesurable
Pour qu'une lésion soit jugée mesurable, au moins une de ses dimensions doit pouvoir être mesurée de façon précise (la dimension la plus longue, dans le plan de la prise de mesures, devra être rapportée).
Pour être mesurables, les lésions doivent présenter une mesure minimum de

- ≥ 10 mm au scanner (pour autant que la largeur de bande du CT-scan soit d'au maximum 5 mm)
- ≥ 10 mm par examen clinique (mesurable par pied à coulisse) (les lésions qui ne peuvent être mesurées précisément doivent être répertoriées comme étant non-mesurables)
- 20 mm par radiographie (=X-ray) du thorax
- Pour qu'un ganglion lymphatique malin soit considéré pathologique et mesurable, celui-ci doit présenter un plus petit axe ≥ 15 mm (le plus petit axe étant l'axe perpendiculaire à la plus grande dimension du ganglion). Seule la longueur de ce plus petit axe sera rapportée tant à l'entrée que durant le suivi.

Maladie non-mesurable
Toutes les autres lésions, incluant les petites lésions (plus grand diamètre < 10 mm au scanner ou les ganglions lymphatiques dont le plus petit axe est ≥ 10 mm et < 15 mm) ainsi que les lésions réellement non-mesurables : maladie leptoméningée, ascite, pleurésie, péricardite, maladie inflammatoire du sein, lymphangites carcinomateuses pulmonaires ou cutanées, les masses abdomino-pelviennes décelées par l'examen clinique mais non confirmées à l'imagerie et les lésions kystiques.
Nota bene : les lésions osseuses, les lésions kystiques simples et les lésions ayant précédemment reçu un traitement local nécessitent une considération particulière (cf commentaires ci-dessous).

Lésions cibles
Les lésions cibles sont sélectionnées parmi les lésions mesurables que présente le malade à l'entrée de l'étude. **Au maximum 5 lésions cibles sont sélectionnées au total avec un maximum de 2 lésions cibles par organe**. La sélection des lésions cibles s'opérera de façon à être représentative de tous les organes envahis, en choisissant les lésions les plus grandes (dans leur plus grande dimension) qui de plus, pourront être suivies tout au long de l'essai avec la méthode utilisée lors de l'examen initial. Les ganglions lymphatiques peuvent être considérés comme lésions cibles si leur plus petit axe (mesuré au scanner) est ≥ 15 mm.

C'est la somme des diamètres de ces lésions cibles (plus grand axe pour les lésions, et plus petit axe pour les ganglions) qui sera suivie au long de l'essai pour évaluer la réponse ou la progression.

Lésions non-cibles
Toutes les autres lésions sont identifiées comme lésions non-cibles et sont également relevées à l'inclusion. Elles ne sont pas mesurées mais sont suivies tout au long de l'essai.

Critères de réponse au traitement :

Lésions cibles :

Réponse complète (RC) : Disparition de toutes les lésions. De plus, tous les ganglions lymphatiques (cible ou non-cible), doivent avoir atteint une dimension < 10 mm dans leur *plus petit* axe.

Attention : les ganglions sélectionnés comme lésions cibles doivent toujours être mesurés (dimension du plus petit axe dans le plan anatomique utilisé pour l'examen BASELINE), même s'ils diminuent en taille durant l'étude et que leur petit axe devient < 10 mm. Dès lors, lorsque des ganglions sont utilisés comme lésion cible, la « somme » des dimensions des lésions n'est pas nécessairement nulle, même en cas de réponse complète, puisqu'un ganglion normal est défini comme ayant un plus petit axe < 10 mm. Pour obtenir une réponse complète chaque ganglion doit avoir atteint une dimension < 10 mm dans son plus petit axe.

Réponse partielle (RP) : Diminution d'au moins 30 % de la somme des diamètres des lésions cibles par rapport à la somme initiale des diamètres (Examen BASELINE).

Progression (PD) : Augmentation ≥ 20 % de la somme des diamètres des lésions cibles par rapport à la plus petite somme des diamètres observée durant l'étude (NADIR), y compris la visite de baseline. En plus de cette augmentation relative de 20%, cette somme doit augmenter d'au moins 0,5 cm.
Nota bene : l'apparition d'une ou plusieurs nouvelles lésions est également considérée comme progression.
Attention : s'il existe une progression par rapport au NADIR et une réponse par rapport à l'examen BASELINE, c'est la progression qui prévaut.

Stabilisation (SD) : Ni RP (ou RC), ni PD.

Lésions non-cibles

Réponse complète : Disparition de toutes les lésions non-cibles et normalisation des marqueurs tumoraux. Tous les ganglions lymphatiques doivent avoir atteint un petit diamètre < 10 mm.
Réponse incomplète - Stabilisation : Persistance d'au moins une lésion non-cible et/ou marqueur tumoral au-dessus des normales.
Progression : Augmentation **indiscutable** de la taille des lésions non-cibles ou apparition d'une nouvelle lésion.

Réponse globale :

Lésions cibles	Lésions non-cibles	Nouvelle lésion		Réponse globale
RC	RC	Non	=	**RC**
RC	Non RC/Non PD	Non	=	**RP**
RC	Non évalué	Non	=	**RP**
RP	Non PD ou pas tous évalués	Non	=	**RP**
SD	Non PD ou pas tous évalués	Non	=	**SD**
Pas tous évalués	Non PD	Non	=	**Non-évaluable**
PD	Indifférent	Oui ou non	=	**PD**
Indifférent	PD	Oui ou non	=	**PD**
Indifférent	Indifférent	Oui	=	**PD**

Commentaires relatifs à la mesurabilité des lésions à l'entrée

Lésions osseuses :

- l'imagerie par scintigraphie osseuse, PET-scan et « plain films » ne sont pas considérées comme étant adéquates pour la mesure des lésions osseuses. Cependant, ces techniques peuvent être utilisées pour confirmer la présence ou la disparition de lésions osseuses
- Les lésions osseuses de type lytique ou de type mélangé lytique-ostéoblastique, qui contiennent une composante identifiable de tissus mous, peuvent être considérés comme des lésions mesurables, pour autant qu'elles puissent être mesurées par des techniques d'imagerie cross-sectionnelle de type CT ou IRM, et que la composante de tissus mous remplissent les conditions de mesurabilité indiquées plus haut.

Lésions kystiques :

- Les lésions qui correspondent au diagnostic de simple kyste par radiographie ne sont pas considérées comme des lésions malignes (ni mesurables, ni non-mesurables)
- Les lésions kystiques de type malin peuvent être prises en compte comme lésion mesurable pour autant qu'elles remplissent les critères de mesurabilité définis plus haut. Cependant, si le patient présente d'autres lésions non kystiques, celles-ci seront préférablement choisies comme lésion cible.

Lésions préalablement traitées localement :

- Les lésions situées dans une région préalablement irradiée ou ayant reçu une autre thérapie loco-régionale ne sont en général pas considérées comme étant mesurables, à l'exception des lésions ayant progressé depuis le traitement local. Le protocole de l'étude doit détailler les conditions spécifiques permettant de considérer de telles lésions comme étant mesurables.

Appendix 13 – Durvalumab dose calculation, preparation and administration

1/ Calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose :

The durvalumab dosing should be done depending on subject weight:
1. Cohort dose: 10 mg/kg
2. Subject weight: Y kg
3. Dose for subject: XY mg = 10 (mg/kg) × Y (kg)
4. Dose to be added into infusion bag:
Dose (mL) = XY mg / 50 (mg/mL)
where 50 mg/mL is durvalumab nominal concentration
The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle only needed for greater than 10% change in weight.
5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL) / 10 (mL/vial)

Example:
1. Cohort dose: 10 mg/kg
2. Subject weight: 80 kg
3. Dose for subject: 800 mg = 10 (mg/kg) × 80 (kg)
4. Dose to be added into infusion bag:
Dose (mL) = 800 mg / 50 (mg/mL) = 16.0 mL
5. The theoretical number of vials required for dose preparation:
Number of vials = 16.0 (mL) / 10 (mL/vial) = 2 vials

2/ The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should not be prepared on the ward.
An additional volume of 0.9% (w/v) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab.
The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.
Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
Vials should be used for specific subjects and should not be shared between subjects.

3/ durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral vein.
Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter.
The IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.
Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.