ETOP 13-18 BEAT-meso

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma

BEAT-meso: Bevacizumab and atezolizumab in malignant pleural mesothelioma

Sponsor and Coordinating Group:

European Thoracic Oncology Platform (ETOP)

EudraCT number: 2018-002180-25

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In collaboration with F. Hoffmann-La Roche Ltd.

Protocol Amendment 2 Signature Page

ETOP 13-18 BEAT-meso

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma

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Principal Investigator Protocol Amendment 2 Signature Page

ETOP 13-18 BEAT-meso

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations. I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by ETOP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial. I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 25 years.

Name of Principal Investigator: _____

Institution's name and place: _____

_____ _____

Signature Date

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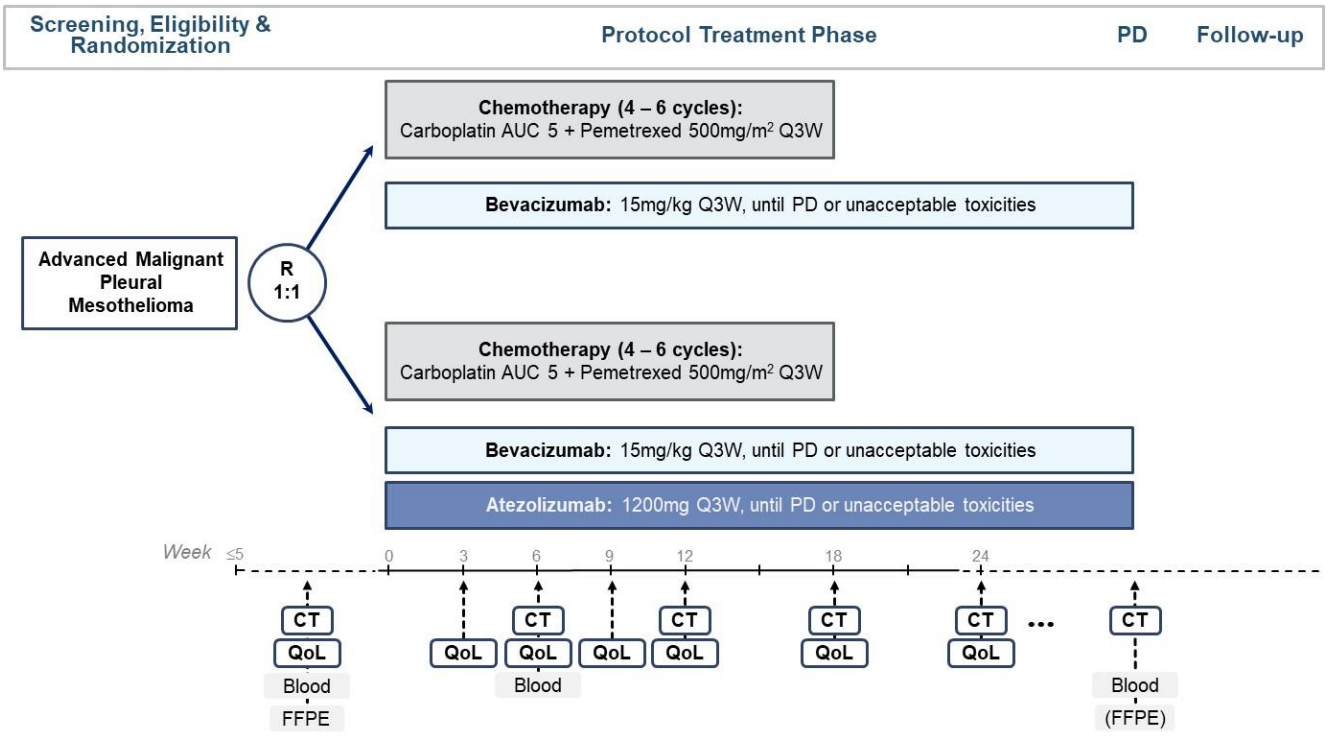
PROTOCOL SUMMARY

ETOP 13-18 BEAT-meso

A multicentre randomised phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma

BEAT-meso: Bevacizumab and atezolizumab in malignant pleural mesothelioma

Sponsor:	European Thoracic Oncology Platform (ETOP)
Pharma partner:	F. Hoffmann-La Roche Ltd.
Population:	Histologically-confirmed advanced malignant pleural mesothelioma (MPM), not amenable for surgery based on local standards (all subtypes are eligible).
Design:	Open-label, randomised two-arm multicentre phase III trial
Sample size:	400 randomised patients



Treatment:

Control arm:

- 4-6 cycles chemotherapy:
  Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W plus
- Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity

Experimental arm:

- 4-6 cycles chemotherapy:
  Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W plus
- Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity plus
- Atezolizumab 1200 mg D1Q3W until PD, refusal or unacceptable toxicity

Rationale:

Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer arising from the mesothelial surface of the pleura. In Europe, the incidence is about 20 per million. Histologic subtypes of MPM include epithelioid (about 60%), and non-epithelioid (around 40%) including sarcomatoid, biphasic and others. This disease is considered resectable in only 10-15% of MPM patients. Currently approved first-line therapy is chemotherapy with cisplatin/pemetrexed with a median overall survival of approximately 12 months [1]. Vascular endothelial growth factor is a key mitogen for MPM cells; targeting angiogenesis, therefore, has a clear rationale in this disease. The addition of bevacizumab to cisplatin/cisplatin plus pemetrexed significantly improved OS (HR=0.77) in the randomised phase III MAPS trial [2]. In the MAPS trial the median OS for the patients in the cisplatin/pemetrexed/bevacizumab arm was 18.8 months. Results from the phase II part of the LUME-MeSO trial showed that the addition of another antiangiogenic agent, nintedanib to cisplatin/pemetrexed improved PFS when compared to cisplatin/pemetrexed (HR=0.56) [3]. The carboplatin/pemetrexed combination is feasible and achieves similar results to cisplatin/pemetrexed [4].

Immunotherapy as monotherapy has now been clinically validated as an effective treatment for many cancers. However, there is room for improvement and for patients with non-inflamed tumours other strategies should be pursued. Tremendous potential exists for synergistic combinations of immunotherapy agents and for combining immunotherapy agents with conventional cancer treatments [5]. Many clinical trials are in progress testing potential synergistic effects of treatments combining immunotherapy with other therapies. A number of models have shown a synergy between anti-angiogenic and immune cell therapies [6]. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma [7]. A study of pembrolizumab plus ramucirumab shows promise in NSCLC [8].

Overall, in MPM the cisplatin/pemetrexed/bevacizumab combination achieves the best results to date. However, new treatment strategies are needed in order to further improve outcome. Immunotherapy in second-line has achieved promising results in a subset of patients with PD-L1-positive tumours and second-line randomised studies are ongoing.

There is a preclinical rationale for combining anti-angiogenic therapies with immunotherapy and clinical studies have already shown promising results. In stage IV non-squamous NSCLC, randomised trials are testing whether the platinum-based/bevacizumab/atezolizumab combination will improve outcome.

The aim of this trial is to address whether the standard therapy in MPM (chemotherapy plus bevacizumab) in combination with an anti-PD-L1 compound (atezolizumab) improves outcome in advanced treatment-naïve MPM patients.

Rationale for the trial design

A 1:1 randomisation will be performed to assess the effect of atezolizumab when added to standard chemotherapy plus bevacizumab as first-line treatment of advanced MPM. The addition of angiogenesis inhibitors to standard chemotherapy has proven to be effective in this setting [2,3], but it is not yet established as standard first-line therapy in all countries, principally due to regulatory and reimbursement issues. Nevertheless, the presence of bevacizumab in both treatment arms will allow the ability to clearly attribute potential differences in OS to the effect of atezolizumab.

The secondary endpoints PFS (investigator assessed), objective response rate, disease control rate, time to treatment failure, duration of response, quality of life and safety, will allow further assessment of the efficacy and safety of atezolizumab when added to standard chemotherapy and bevacizumab.

References

1. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21(14): 2636-44.
2. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016; 387(10026): 1405-14.
3. Scagliotti GV, Gaafar R, Nowak A, et al. P2.01: LUME-MeSO: Phase II/III Study of Nintedanib + Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Track: SCLC, Mesothelioma, Thymoma. J Thorac Oncol 2016; 11(10S): S216.
4. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer 2013; 109(3): 552-8.
5. Melero I, Berman DM, Aznar MA, Korman AJ, Perez Gracia JL, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. Nat Rev Cancer 2015; 15(8): 457-72.
6. Soto-Ortiz L, Finley SD. A cancer treatment based on synergy between anti-angiogenic and immune cell therapies. J Theor Biol 2016; 394: 197-211.
7. Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun 2016; 7: 12624.
8. Herbst RS, Martin-Liberal J, Calvo E, et al. Interim safety and clinical activity in patients with advanced NSCLC from a multi-cohort phase 1 study of ramucirumab (R) plus pembrolizumab (P). Ann Oncol 2016; (2016) 27 (suppl_6): LBA38.

Objectives and endpoints:

Objective

The objective of this trial is to assess the effect of atezolizumab in terms of OS when added to standard of care (carboplatin/pemetrexed/bevacizumab), as first-line treatment of advanced MPM.

Primary endpoint

- Overall survival

Secondary endpoints

- Progression-free survival (investigator assessed)
- Objective response rate
- Disease control rate
- Time to treatment failure
- Duration of response
- Safety and tolerability
- Quality of life

Correlative endpoints:

Responses according to:

- PD-L1 expression levels
- Tumour mutational burden

Most important inclusion criteria (see Section 7.1 for complete list):

- Histologically confirmed advanced malignant pleural mesothelioma (all histological subtypes are eligible)
- Able to understand and give written informed consent and comply with trial procedures
- Age ≥18 years
- Performance Status 0-1
- Not amenable for radical surgery based on local standards
- Availability of tumour tissue for translational research
- Evaluable disease or measurable disease as assessed according to the mRECIST v1.1
- Life expectancy ≥3 months
- Adequate haematological, renal (CrCl >45) and liver function
- Completed baseline QoL questionnaire
- Men and women of childbearing potential must agree to use adequate contraception

Most important exclusion criteria (see Section 7.2 for complete list):

- Prior treatment for malignant pleural mesothelioma
- Active autoimmune disease that has required systemic treatment in the past 2 years
- Previous history of significant haemoptysis (defined as at least 2.5mL emission of red blood) within 3 months prior to inclusion.
- Recent surgery:
  - Major surgery or significant traumatic injury 28 days prior to the first dose of bevacizumab.
  - Minor surgical procedure within 7 days, or placement of a vascular access device 2 days prior to the first dose of bevacizumab.
- HIV or active hepatitis B or hepatitis C

Statistical considerations:

The efficacy of atezolizumab, when given with bevacizumab plus standard chemotherapy, will be evaluated based on the primary endpoint of OS, which will be compared between randomised treatment groups. An interim analysis will be performed at approximately 75% information time, based on O'Brien-Fleming boundaries calculated by the Lan-DeMets spending function.

Comparison of OS between the two arms

The target median OS for patients treated with atezolizumab plus bevacizumab and chemotherapy is 24 months, i.e., an absolute increase of 7 months compared to a median OS of 17 months for patients treated with bevacizumab and chemotherapy alone.

Using the log-rank test at a one-sided significance level of 2.5%, a total of 284 OS events are required, in the final OS analysis, to detect the targeted increase of 7 months in the median OS (HR=0.708) with 82.1% power.

Based on an accrual rate of 8 patients per month for the first 15 months and 20 patients per month thereafter, a total of 400 randomised patients, 200 in each treatment group, are needed to be followed for an expected maximum duration of 58 months so as to observe the required number of OS events.

Stratification factors:

- Pure epithelioid vs not
- Stage IV (according to 8th TNM classification) versus others

Interim analysis

An efficacy interim analysis for OS will be performed when approximately 213 OS events (75% of the required events) have been observed. This is expected to occur approximately 42 months after the randomisation of the first patient. If the boundary is crossed at the interim analysis,

superiority of the experimental treatment will be claimed and we can proceed to reporting this result as the primary analysis.

Total trial duration:

Clinical visits (until the required 284 OS events for the primary endpoint are recorded) are expected to span approximately 58 months after randomisation of the first patient, assuming an accrual period of 29 months. In addition, a start-up period of 6 months is estimated, as the trial is activated by participating centres. The primary analysis will be available approximately 6 years after the inclusion of the first patient.

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
AR	Adverse Reaction
ASBI	Average Symptom Burden Index
AST	Aspartate Transaminase
ATE	Arterial Thromboembolism
CHF	Congestive heart failure
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-limiting Toxicities
DoR	Duration of Response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
EoT	End of Treatment
ERB	Ethical Review Board
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed, Paraffin Embedded
FGFR	Fibroblast Growth Factor Receptor
FWER	Family-Wise Error Rate
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
LCSS	Lung Cancer Symptom Scale

LCSS-Meso	Lung Cancer Symptom Scale-Mesothelioma
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LFU	Lost to Follow-up
MPM	Malignant Pleural Mesothelioma
mRECIST	updated modified RECIST criteria for mesothelioma
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Carcinoma
ONJ	Osteonecrosis of the Jaw
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PDGFR	Platelet-derived Growth Factor Receptor
PD-L1	Programmed Cell Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PIS	Patient Information Sheet
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response Rate
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNM	Tumour, Nodes, and Metastases
TSH	Thyroid Stimulating Hormone
TTF	Time-to-Treatment Failure
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normal Lab Value
VAS	Visual Analogue Scales
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell Count
WC	Withdrawal of Consent

TRIAL SCHEDULE

	Before randomisation[1]	**Treatment Period**[2]		**PD**[4]	**EoT**	**Post treatment visit**	
		Control arm[3]	Experimental arm[3]			Before PD Every 6 weeks ±4 days	After PD Every 12 weeks ±3 weeks
Written informed consent: before any trial specific evaluations and intervention[5]							
Medical history: smoking history, asbestos exposure, employment history, comorbidities and allergies							
Demographics: Year of birth, gender, race							
Vital signs: PS, blood pressure, heart rate, temperature, body weight and height (only at baseline)		At each cycle, within 3 days before treatment administration					
Baseline symptoms[6]							
Adverse events[6]							
Concomitant medications[7]							
Pathology report[8]							
QoL[9]		Within 3 days before treatment administration in cycles 2-5 and cycles 7 and 9					
Survival and further lines of treatment[10]							
Laboratory tests							
Thyroid function:[11] TSH, with reflex free T3/4			Every 4th cycle, within 3 days before treatment administration				
HIV test / hepatitis B/C							
Pregnancy test[12]							
Chemistry: serum albumin, glucose, potassium, sodium, calcium, magnesium, amylase and lipase		At each cycle, within 3 days before treatment administration					
Haematology: haemoglobin, platelet count and white blood cell count, including differential (lymphocytes and absolute neutrophil count)		At each cycle, within 3 days before treatment administration					

	Before randomisation[1]	**Treatment Period**[2]		**PD**[4]	**EoT**	**Post treatment visit**	
		Control arm[3]	Experimental arm[3]			Before PD Every 6 weeks ±4 days	After PD Every 12 weeks ±3 weeks
Coagulation profile (INR)		At every 2nd cycle, within 3 days before treatment administration					
Liver function tests: total bilirubin, ALT, AST, ALP, GGT, and LDH		At each cycle, within 3 days before treatment administration					
Renal function tests: urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault		At each cycle, within 3 days before treatment administration					
Urine analysis: pH, specific gravity, glucose, protein, ketones and blood, dipstick permitted[13]		At every 2nd treatment cycle, within 3 days before treatment administration					
Treatment							
Atezolizumab (1200mg, Q3W)[14][4]							
Bevacizumab (15mg/kg, Q3W)[14][4]							
Chemotherapy: Carboplatin AUC 5 plus pemetrexed 500 mg/m^2, D1Q3W, for 4-6 cycles							
Further lines of treatment[10]							
Disease evaluation							
Radiological tumour assessment[15]					(16)	(17)	
Biological material							
FFPE tumour material[18]				Re-biopsy strongly recommended			
Blood samples[19]	(20)	At cycle 3, within 3 days before treatment administration (19)					

Mandatory evaluation / intervention

(1) Evaluations to be done within 5 weeks before randomisation. If examinations were done prior to 5 weeks before start of randomisation, they have to be repeated.
(2) Every 3 weeks (±3days). The protocol treatment for both arms should begin on the day of randomisation or as close as possible to this date (preferably within 7 days after randomisation).
(3) Assessments have to be done at every cycle, within 3 days before treatment administration.
(4) Patients are considered to be on protocol treatment for as long as they receive either chemotherapy, bevacizumab and/or atezolizumab
(5) Written informed consent: within 6 weeks prior to randomisation
(6) Adverse event reporting: Adverse events have to be reported on the adverse event form, from the date of signature of informed consent until 90 days after the last dose of protocol treatment. Symptoms present at baseline will be recorded on the adverse event form as well
(7) All Concomitant medications or therapies for comorbidities that are used by a patient at baseline within 14 days prior to randomisation should be recorded. During protocol treatment, in case of an AE or SAE, all concomitant medication used to treat the event must be reported.
(8) A copy of the pathology report (from the diagnostic biopsy at baseline and from re-biopsy at progression) should be uploaded in ETOPdata (all information allowing identification of the patient, e.g., patient's name, day and month of birth, must be removed and the ETOP patient identification number added)
(9) Quality of Life. At baseline before randomisation, and within 3 days before treatment administration in cycles 2-5 (e.g., at weeks 3, 6, 9 and 12) and cycles 7 and 9 (e.g., at weeks 18 and 24) **OR** until end of protocol treatment, whatever is first. It is important that the QoL questionnaire is completed before any diagnostic procedures or communication of diagnostic or prognostic information to the patient, and before trial treatment is given. Upload copy of the QoL form to ETOPdata after each assessment.
(10) Survival status and further lines of treatment: to be collected during the follow-up visits.
(11) Thyroid function test: TSH, free T3 (or total T3 if free T3 is not performed per local standard), and free T4 at baseline. For patients in the experimental arm thyroid function test is repeated at cycle 1, within 3 days before treatment administration and thereafter every 4th treatment cycle (i.e., cycles 5, 9, 13, etc.; within 3 days before treatment administration), for as long as the patient receives atezolizumab.
(12) Pregnancy test: Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum pregnancy test within 2 weeks before randomisation. Pregnancy testing has to be repeated during the duration of protocol trial treatment according to local practice. Women of childbearing potential and sexually active men must use highly effective contraception (methods that result in a failure rate of <1% per year) from the start of protocol treatment until at least 6 months after the last dose (see Section 9.7 for highly effective contraception methods). Any pregnancy occurring during treatment or within 6 months following the last dose of protocol treatment must be reported including its outcome (see Section 15.6.19).
(13) For as long as the patient is receiving bevacizumab, for urine dipstick reading for protein 2+ or higher, patient should undergo further assessment with a 24-hour urine collection. Bevacizumab may only be administered if result is <2g/24 hours.
(14) Treatment continues until progression according to the mRECIST v1.1 or lack of tolerability, or patient declines further treatment.
(15) Radiological tumour assessment: by contrast enhanced CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included, preferred) or alternatively (and only after the first CT at baseline) contrast enhanced CT of thorax and ultrasonography of upper abdomen, following the schedule indicated below; until tumour progression determined according to the mRECIST v1.1. The same imaging technique, acquisition, and processing parameters should be used for each patient throughout the trial.

- At baseline: within 5 weeks before randomisation
- During protocol treatment: every 6 weeks (42 days) from start of protocol treatment, e.g., at week 6, 12, 18, 24, …(±4 days)

(16) CT to be repeated if not done within 6 weeks prior to end of treatment visit.
(17) In case of treatment stop for reason other than progressive disease, CT needs to be repeated every 6 weeks (±4 days) until progression.
(18) Mandatory FFPE tumour material: Archival tumour or fresh biopsy sample taken >7 days prior to protocol treatment start is required. An FFPE tumour tissue block is requested. Only if the block is not available, 15 slides of 4-5 µm thickness are an acceptable alternative to the block. Cytological specimens are not accepted in this trial. If slides are submitted in lieu of the block, they must be freshly cut and shipped to the central reference laboratory within 1 week of sectioning. Additional FFPE material, beyond what is listed above is also requested for translational research and is described in Section 12.3. A biopsy at progression is strongly recommended and also additional slides if the baseline block was not submitted.
(19) Blood samples:

At baseline:	2.5 mL whole blood for DNA analysis / 2.5 mL whole blood for RNA analysis / serum sample from 5 mL blood
At cycle 3 (within 3 days before treatment administration):	2.5 mL whole blood for RNA analysis / serum sample from 5 mL blood
At disease progression:	2.5 mL whole blood for RNA analysis / serum sample from 5 mL blood

(20) Sample may be taken after randomization but must be taken before treatment administration in cycle 1.

BACKGROUND AND RATIONALE

1. Background

1.1. Disease background

1.1.1. Malignant pleural mesothelioma

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy arising from the mesothelial surface of the pleura. In Europe, the incidence is about 20 per million and is almost always caused by asbestos exposure, with a usual lag time of 30 years between exposure and presentation.[1] Histologic subtypes of MPM include epithelioid (about 60%), and non-epithelioid (around 40%) including sarcomatoid, biphasic and others. Disease is considered resectable in only 10-15% of MPM patients.[2] The prognosis in unresectable cases remains very poor, with median survival of 9 to 12 months.[1,3] The disease is invariably fatal, due to anatomical limitations preventing the achievement of a complete microscopic surgical resection and tumour relative chemo-refractoriness.[4]

Despite decades of clinical research, cytotoxic chemotherapy remains one of the few therapeutic options that has been proven to improve survival in advanced MPM in a randomised controlled trial.[5] The combination of cisplatin and pemetrexed has become standard first-line therapy worldwide for patients who are not suitable for aggressive surgery or in whom chemotherapy is recommended as part of a multimodality regimen.[4]

Cisplatin/pemetrexed is associated with a response rate of 30-40% and confers an OS advantage of 3 months over cisplatin alone, and is the only licensed systemic therapy for mesothelioma.[3]

Carboplatin is often substituted for cisplatin, due to simpler and shorter administration and assumption of a more favourable toxicity profile based on experience in other diseases. Although carboplatin use is not supported by randomised evidence, and there has been no direct comparison between the two platinum agents, phase I and II studies have demonstrated similar activity of either carboplatin or cisplatin with pemetrexed, with objective radiological response rates between 20% and 30%.[6,7]

1.2. Treatment background

1.2.1. Atezolizumab

Atezolizumab (RO5541267, trade name Tecentriq®) is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumour-specific T-cell responses, resulting in improved anti-tumour activity.[8,9] Atezolizumab has minimal binding to Fc-

receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T-cells.

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

1.2.2. Bevacizumab

Bevacizumab (Trade name Avastin®) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the interaction of Vascular Endothelial Growth Factor-A (VEGF-A) to its receptors [Flt-1 and Kinase Insert Domain Receptor (KDR)] on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in-vitro models of angiogenesis. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth. Administration of bevacizumab to xenotransplant models of colon cancer in nude mice caused reduction of microvascular growth and inhibition of metastatic disease progression.[10,11]

Angiogenesis plays an important role in MPM. Several studies have shown that mesothelioma cell lines, as compared to the normal mesothelial cells and fibroblasts, produce high amounts of proangiogenic factors, including VEGF. Mesothelioma cells also express VEGFR-1 and VEGFR-2 and respond to VEGF in the environment by increasing cell proliferation. In addition, blocking the VEGFRs with a monoclonal antibody inhibits mesothelioma cell growth. This implicates VEGF as not only a promoter of angiogenesis, but also an autocrine growth factor for mesothelioma cells.[12]

The addition of bevacizumab to cisplatin/cisplatin plus pemetrexed significantly improved OS (HR=0.77) in the randomised phase III MAPS trial.[12] In the MAPS trial the median OS for patients in the cisplatin/pemetrexed/bevacizumab arm was 18.8 months.

The carboplatin/pemetrexed/bevacizumab combination is feasible and achieves similar results to cisplatin/pemetrexed/bevacizumab.[7]

In addition, the LUME-MeSO trial evaluated the addition of another antiangiogenic agent, nintedanib, a tyrosine kinase inhibitor targeting the receptors VEGFR, Fibroblast Growth Factor Receptor (FGFR) and Platelet-derived Growth Factor Receptor (PDGFR), to cisplatin/pemetrexed. The combination improved PFS when compared to cisplatin/pemetrexed (HR=0.56) in the phase II part of the trial.[13]

1.2.3. Atezolizumab in combination with bevacizumab

There is a strong scientific rationale to support the combination of immune-checkpoint blockade and VEGF inhibition. While blockade of the PD-L1 to PD-1 interaction is

responsible for restoring anti-cancer immunity, VEGF inhibition can enhance this effect by promoting the T-cell tumour infiltration.

The combination of immune-checkpoint inhibitors and bevacizumab has already been assessed in several trials in the non-squamous non-small-cell lung cancer (NSCLC) setting.

The phase I/II trial Checkmate 370 evaluated the efficacy and safety of first-line nivolumab administered alone or in combination with standard-of-care maintenance therapy, including bevacizumab for NSCLC (cohort A, non-squamous).[14]

Similarly, the phase I/II trial Keynote 021 evaluated the efficacy and safety of pembrolizumab when added to various chemotherapy regimens including bevacizumab for NSCLC (cohort B, non-squamous).[15]

The phase III IMPOWER150 trial tested this combination therapy as first-line treatment in advanced non-squamous NSCLC. Comparison between chemotherapy plus atezolizumab plus bevacizumab, and chemotherapy plus bevacizumab alone showed that the addition of atezolizumab to bevacizumab and chemotherapy was superior to bevacizumab and chemotherapy alone, irrespective of PD-L1 expression.[16]

Moreover, the safety profile of the atezolizumab and bevacizumab plus chemotherapy combination was consistent with the safety profiles of the individual medicines, and no new safety issues emerged.

1.3. Quality of life

Patients with advanced MPM often experience serious disease symptoms including fatigue, dyspnoea, loss of appetite, cough and pain, which can adversely affect patients' quality of life (QoL).[17-20] Most patients present with three or more of these symptoms and they vary among patients.[18-21]

In the MAPS trial, a significantly greater proportion of patients with unresectable MPM who received bevacizumab in addition to pemetrexed/cisplatin as first-line treatment reported an improvement in fatigue nine weeks after the baseline assessment compared to those receiving pemetrexed/cisplatin without bevacizumab.[12] In addition, a smaller proportion of patients receiving bevacizumab reported a significant worsening in daily activities. The proportion of patients reporting an improvement in dyspnoea, cough, and pain was similar with or without bevacizumab. A further QoL analysis of this trial showed that the addition of bevacizumab significantly improved QoL deterioration-free survival (QFS) for the domain peripheral neuropathy and a trend for a delay in pain worsening.[22]

Adding atezolizumab to systemic chemotherapy (platinum combined with pemetrexed) and bevacizumab may cause additional immuno-related side effects. On the other hand, patients may also experience further improvement in tumour-related symptoms, in particular for pain and dyspnoea. Given the limited survival time of patients with advanced MPM, balancing the trade-offs between treatment efficacy and side effects is a key issue, and symptom-specific and global QoL is an important outcome.

2. Trial rationale and benefit-risk assessment

2.1. Trial rationale

A 1:1 randomisation will be performed to assess the effect of atezolizumab when added to standard chemotherapy plus bevacizumab as first-line treatment of advanced MPM. The addition of angiogenesis inhibitors to standard chemotherapy has proven to be effective in this setting,[12,13] but it is not yet established as standard first-line therapy in all countries. Nevertheless, the presence of bevacizumab in both treatment arms will allow the clear attribution of potential differences in median OS to the effect of atezolizumab.

This strategy allows testing of a potentially innovative and optimized multimodal combination in this disease, where very few advances characterise the last decades.

The secondary endpoints PFS (investigator assessed), objective response rate, disease control rate, time to treatment failure, duration of response and safety, will allow further assessment of the addition of atezolizumab to standard chemotherapy and bevacizumab.

2.2. Benefit-Risk Assessment

This trial will enrol patients with advanced MPM. Given the poor prognosis and the limited treatment options for these patients, representing a strict unmet need, this population is considered ideal for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with bevacizumab plus standard chemotherapy is expected to be acceptable in this setting and we expect that the potential benefit might outweigh the additional risks from the combination treatment.

OBJECTIVES AND ENDPOINTS

3. Objectives

3.1. Primary objective

The objective of this trial is to assess the effect of atezolizumab in terms of OS when added to standard of care (carboplatin/pemetrexed/bevacizumab), as first-line treatment of advanced MPM.

3.2. Secondary objectives

3.2.1. To evaluate secondary measures of clinical efficacy including investigator assessed PFS, objective response rate, disease control rate, time to treatment failure, duration of response.

3.2.2. To assess the safety and tolerability of the treatment.

3.2.3. To evaluate symptom-specific and global quality of life.

4. Endpoints

4.1. Primary endpoint

4.1.1. Overall survival

4.2. Secondary endpoints

4.2.1. Progression-free survival (investigator assessed) according to the mRECIST v1.1

4.2.2. Objective response rate

4.2.3. Disease control rate

4.2.4. Time to treatment failure

4.2.5. Duration of response

4.2.6. Adverse events according to CTCAE v5.0

4.2.7. Symptom-specific and global quality of life

4.3. Correlative studies

Further exploratory analyses include responses according to PD-L1/L2 expression level and tumour mutational burden.

4.4. Endpoint definition

4.4.1. Overall survival

Overall survival (OS), the primary endpoint, is defined as the time from the date of randomisation until death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients without post-baseline information will be censored at the date of randomization (plus 1 day).

4.4.2. Progression-free survival (investigator assessed)

PFS is defined as the time from the date of randomisation until documented progression (according to the mRECIST v1.1) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the date of last tumour assessment. Patients without a post-baseline tumour assessment will be censored at the date of randomization (plus 1 day).

4.4.3. Objective response rate

Objective response rate (ORR) is defined as the percentage of patients that achieve a best overall response [complete response (CR) or partial response (PR)] according to the mRECIST v1.1 (see Section 10.1 and Appendix 2) across all post-randomization time-points until (i) the end of protocol treatment or, as an alternative approach, (ii) until the end of follow-up. Confirmation of response will not be required.

4.4.4. Disease control

Disease control (DC) is defined as complete or partial response, or disease stabilisation at 24 weeks.

4.4.5. Time-to-Treatment Failure

Time-to-Treatment Failure (TTF) is defined as the time from the date of randomisation to discontinuation of protocol treatment for any reason (including progression of disease, death, discontinuation of at least one of the drugs consisting the treatment combination due to any reason, such as toxicity or refusal). Censoring will occur at the last follow-up date.

4.4.6. Duration of response

Duration of Response (DoR) is defined as the interval from the date of first documentation of objective response (CR or PR, according to the mRECIST v1.1) to the date of first documented progression/relapse or death.

4.4.7. Toxicity

All safety parameters will be summarised in tables to evaluate the safety profile of the protocol treatment in terms of:

- Adverse events (any-cause as well as treatment-related) including adverse events leading to dose interruptions, withdrawal of protocol treatment, and death
- Severe, serious, and selected adverse events
- Deaths
- Laboratory parameters and abnormalities, and vital signs

4.4.8. Quality of life

QoL will be assessed by the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) an 8-item questionnaire including five symptoms (i.e., appetite loss, fatigue, cough, dyspnoea, and pain) and three items addressing symptomatic distress, normal activity, and global QoL.[18,21,23] The primary QoL endpoint will be the change in the LCSS total score (average of all 8 items) from baseline to 12 weeks after treatment start.

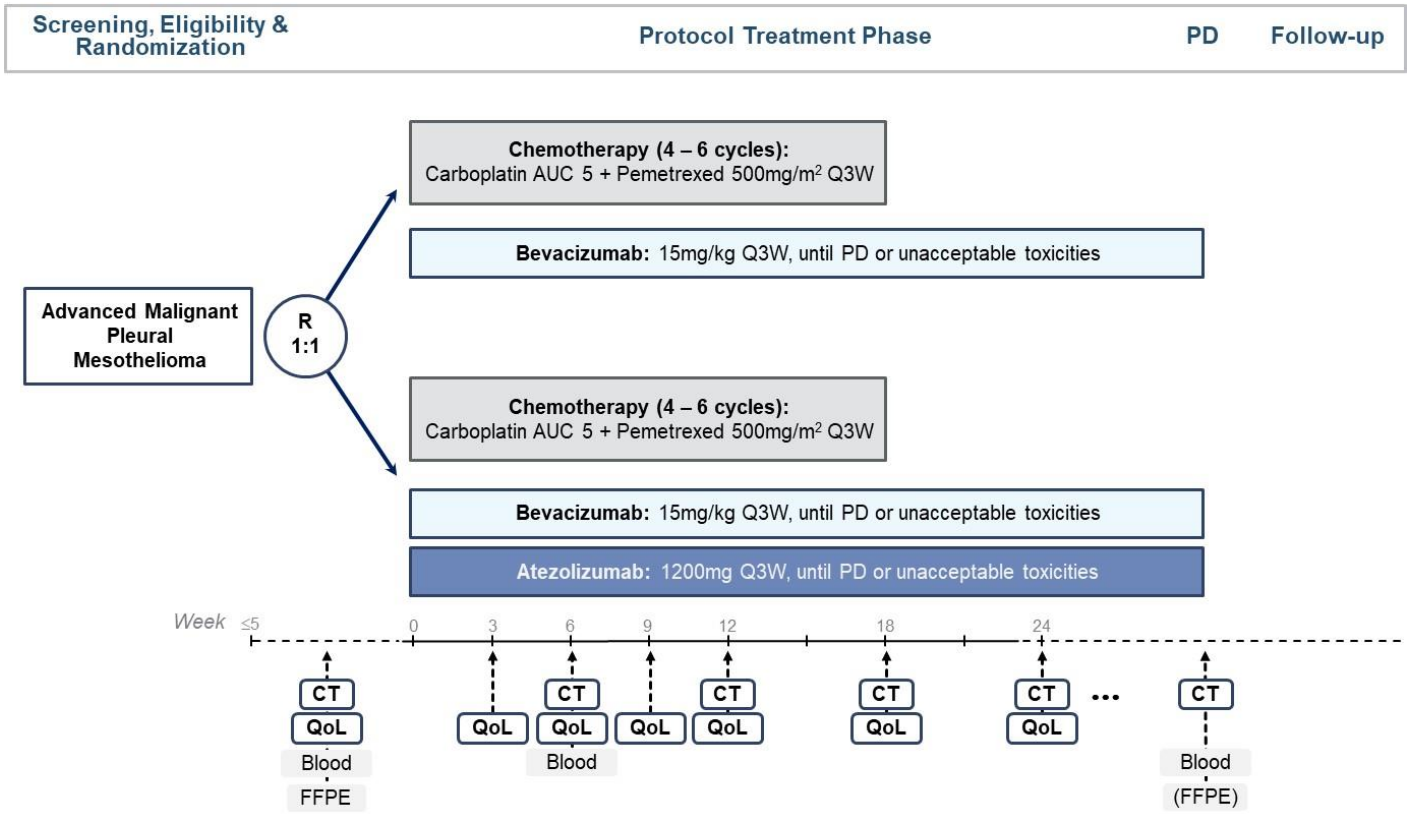
All items are measured by visual analogue scales (VAS) using 100-mm lines to assess the intensity of patient responses addressing the time frame of the past day (operationalized: last 24 h). Each item is assigned an individual score corresponding to the length of the line representing intensity as marked by the patient (with 0 as the lowest and 100-mm as the highest rating).

An average of all eight items is used for a total score. A sub-score using the mean of all five major symptoms or "average symptom burden index" (ASBI), the single global QoL item, and/or individual items to report specific areas of change can be used.

TRIAL DESIGN AND TRIAL DURATION

5. Trial design

BEAT-meso is a two-arm, randomised, open-label multicentre phase III trial, with an interim efficacy analysis, evaluating the activity of atezolizumab when added to standard of care (carboplatin /pemetrexed/bevacizumab), as first-line treatment of advanced MPM.



5.1. Rationale for trial design

5.1.1. Rationale for atezolizumab dose and schedule

Atezolizumab will be administered at a fixed dose of 1200 mg i.v. Q3W (1200 mg on day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumour activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities (DLTs) were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies[24] and available clinical pharmacokinetic, efficacy, and safety data (refer to the ***Atezolizumab Investigator's Brochure*** for details).

5.1.2. Rationale for bevacizumab dose and schedule

Bevacizumab will be administered at 15 mg/kg by i.v. Q3W, which is the recommended dosage for bevacizumab in NSCLC in combination with chemotherapy. Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

The highest bevacizumab dose tested in humans was 20 mg/kg of body weight Q2W. This dose was associated with severe migraine in several patients. Please refer to the ***Bevacizumab Investigator's Brochure*** and the Summary of Product Characteristics for details.

5.1.3. Rationale for patient population

This trial will randomise patients with advanced MPM, regardless of PD-L1 expression. Despite decades of clinical research, the prognosis of unresectable, advanced MPM remains very poor, with a median survival of 9-12 months.[1,3]

Tumour-cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumour antigens. Boosting tumour specific T-cell immunity in this setting by blocking the PD-L1 pathway may result in deeper and more durable responses than those observed with standard chemotherapy alone, and this may reasonably occur in tumours regardless of PD-L1 expression. Of importance, phase II data have demonstrated promising activity in late line treatment of mesothelioma, with no predictive ability of PD-L1 shown to date.[25-27]

5.1.4. Rationale for control group

For patients with MPM, systemic chemotherapy (platinum combined with pemetrexed), in combination with surgery if considered appropriate, remains the international standard of care.[4] In the context of unresectable disease, cisplatin/pemetrexed is associated with a response rate of 41% and confers an OS advantage of 3 months over cisplatin alone, and is the only licensed systemic therapy for mesothelioma.[3]

Despite the significant improvement in OS with the addition of bevacizumab to chemotherapy in the MAPS trial,[12] bevacizumab is still not yet approved as standard therapy in MPM. Nevertheless, the presence of bevacizumab in both treatment arms will allow clear attribution of a potential difference in median OS to the effect of atezolizumab.

5.1.5. Rationale for an open-label trial

In order to facilitate patient care in the context of a long treatment period, an open-label trial design was chosen. This supports the fast and specific management of potential known toxicities associated with atezolizumab. Both patients assigned to the atezolizumab-containing arm, as well as treating physicians may be capable of suspecting immune-mediated adverse events.

The primary endpoint of OS limits the impact of investigator biased interpretation of disease response.

To ensure the validity of data collected in this open-label trial the trial statistician preparing the aggregate data for analysis will be blinded to the treatment assignment. In addition, the strategy and timing for the final analysis of the primary endpoint, including censoring rules and methods for handling missing data, are pre-specified in the protocol. A statistical analysis plan, describing the statistical techniques for the trial analyses (interim and final) in detail will be developed before the corresponding interim and final database locks and the beginning of the analyses.

5.1.6. Rationale for OS as primary endpoint

In this trial, the primary efficacy endpoint will be OS. This trial will test the hypothesis that addition of atezolizumab to standard chemotherapy plus bevacizumab will prolong OS compared to standard chemotherapy plus bevacizumab alone.

Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced MPM. Recent data also suggest that OS may be a more sensitive endpoint for cancer immunotherapy than PFS.

For example, in the randomised phase II POPLAR trial, patients with advanced NSCLC in the intent-to-treat (ITT) population had a significant improvement in OS when treated with atezolizumab compared with docetaxel, with a stratified hazard ratio (HR) of 0.73 (95% CI: 0.53, 0.99). PFS in the ITT population was similar in the two treatment arms: HR of 0.94 (95% CI: 0.72, 1.23).[8]

The BEAT-meso trial has been designed to detect a substantial magnitude of benefit in the intention-to-treat population, that is, a significant improvement in median OS from 17 months in the control arm to 24 months in the experimental arm, corresponding to a target OS HR of 0.708.

5.1.7. Rationale for choice of QoL questionnaire and assessment intervals

Currently, only two QoL measures have been validated for use in mesothelioma patients, the EOTRC QLQ-C30 and its lung cancer-specific module QLQ LC-13[28] and a modified version of the LCSS, the LCSS-Meso.[18,21,23] The LCSS-Meso focuses primarily on the physical and functional dimensions of QoL by addressing the most common symptoms experienced by mesothelioma patients (appetite loss, fatigue, cough, dyspnoea, and pain), with other dimensions captured in less depth through three global items for symptomatic distress, normal activity and global QoL.

Compared to the QLQ-C30 and the QLQ-LC13 with a total of 43 items, the LCSS-Meso covers the main symptoms and global QoL aspects relevant in this population with eight items. The two questionnaires do not include side-effects related to immunotherapy. The MAPS trial used the QLQ-C30 and the LCSS-Meso, which have partly overlapping content. Differences between groups favouring the cisplatin/pemetrexed/ bevacizumab arm were found for fatigue using the QLQ-C30 and for the impact on normal activities and symptom distress using the LCSS-Meso.[12] Given these results and taking into consideration that patients are in a palliative situation receiving a rather burdensome treatment regimen, the burden of completing QoL questionnaires should be kept to a minimum.

Therefore, the use of the LCSS-Meso seems reasonable in this setting. A brief questionnaire also allows for more frequent assessments (i.e. 3-weekly during the first 12 weeks). QoL assessments every 3-weeks provides data similar to more frequent evaluations, whereas less frequent assessments (every 4 or every 6 weeks) may provide data which is below the recommended minimum adequacy rate.[23] Therefore, QoL will be assessed every three weeks

for the first three months of treatment, followed by two assessments at 18 and 24 weeks after randomisation.

6. Sample size and trial duration

A total of 400 randomised patients are needed, 200 in each treatment group. The patients will be recruited from approximately 30 centres in eight European countries.

Clinical visits (until the required events for the primary endpoint are recorded) are expected to span approximately 58 months after randomisation of the first patient, assuming an accrual period of 29 months. In addition, a start-up period of 6 months is estimated, as the trial is activated by participating centres. The primary analysis will be available approximately 6 years after the inclusion of the first patient.

MATERIAL AND METHODS

7. Patient selection

Written informed consent must be signed and dated by the patient and the investigator prior to any trial-related intervention including the submission of mandatory biomaterial.

7.1. Inclusion criteria

7.1.1. Histologically confirmed advanced malignant pleural mesothelioma (all histological subtypes are eligible)

7.1.2. Not amenable for radical surgery based on local standards

7.1.3. Evaluable disease or measurable disease as assessed according to the mRECIST v1.1

7.1.4. Availability of tumour tissue for translational research. Either archival tumour or fresh biopsy sample taken >7 days prior to protocol treatment start.

7.1.5. Age >18 years

7.1.6. Performance Status 0-1

7.1.7. Life expectancy >3 months

7.1.8. Adequate haematological function:

- Haemoglobin ≥90 g/L or ≥5.6 mmol/L
- WBC ≥1.0× 10^9/L
- Lymphocytes ≥0.5× 10^9/L
- Absolute neutrophil count (ANC) ≥1.5× 10^9/L
- Platelet count ≥100× 10^9/L

7.1.9. Adequate renal function:

- Calculated creatinine clearance ≥45 mL/min (according to Cockcroft-Gault)

Cockcroft-Gault formula version with mg/dL:

$$\frac{\text{mL}}{\text{min}} = \frac{(140\text{-age[years]}) \times \text{actual body weight [kg]}}{72 \times \text{Creatinine}_{\text{serum}} \left(\frac{\text{mg}}{\text{dL}}\right)} \text{ (×0.85 if female)}$$

Cockcroft-Gault formula version with µM:

$$\frac{\text{mL}}{\text{min}} = \frac{(140\text{-age[years]}) \times \text{actual body weight [kg]}}{\text{Creatinine}_{\text{serum}}\ [\mu\text{M}]} \times \text{A}$$

A= 1.23 [male] and 1.04 [female]

- Proteinuria <2+ (dipstick) or ≤1.0 g of protein in a 24-hour urine collection

7.1.10. Adequate liver function:

- ALT and AST ≤2.5× ULN. If the patient has liver metastases, ALT and AST must be ≤5× ULN
- Total bilirubin ≤1.5x ULN. If the patient has liver metastases or documented Gilbert's syndrome (unconjugated hyperbilirubinaemia) ≤3x ULN.

7.1.11. Able to understand and give written informed consent and comply with trial procedures

7.1.12. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum pregnancy test within 2 weeks before randomisation.

7.1.13. Baseline QoL form has been completed

7.1.14. Written Informed Consent for protocol treatment must be signed and dated by the patient and the investigator prior to any trial-related intervention.

7.2. Exclusion criteria

7.2.1. Prior treatment for malignant pleural mesothelioma. Prior radiotherapy for symptom control is allowed, but the irradiated lesion cannot be used as target lesion. If the patient has another target lesion, the patient is eligible.

7.2.2. Treatment with systemic immune-stimulatory agents (including but not limited to interferons, interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomisation and during protocol treatment.

7.2.3. Treatment with systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumour necrosis factor [anti-TNF] agents) within 2 weeks prior to randomisation and during protocol treatment. Patients who have received acute, low-dose (≤10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the trial.

7.2.4. Previous allogeneic tissue/solid organ transplant

7.2.5. Live vaccines within 4 weeks prior to first dose of protocol treatment

7.2.6. Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg). Anti-hypertensive therapy to achieve adequate control is allowable.

7.2.7. Prior history of hypertensive crisis or hypertensive encephalopathy.

7.2.8. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomisation

7.2.9. History of haemoptysis (≥one-half teaspoon of bright red blood per episode) within 1 month prior to randomisation

7.2.10. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)

7.2.11. Current or recent (within 10 days before randomisation) use of aspirin (>325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol

7.2.12. Current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable for >2 weeks prior to randomisation.

Permitted:

- The use of full-dose oral or parenteral anticoagulants, as long as the INR or aPTT is within therapeutic limits (according to the local medical standard) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to randomisation.
- Prophylactic anticoagulation for the patency of venous access devices, provided the activity of the agent results in an INR <1.5× ULN and aPTT is within normal limits within 2 weeks prior to randomisation.
- Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day)

7.2.13. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab

- Major surgery or significant traumatic injury 28 days prior to the first dose of bevacizumab.
- Minor surgical procedure within 7 days, or placement of a vascular access device 2 days prior to the first dose of bevacizumab.

7.2.14. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to randomisation

7.2.15. Clinical signs of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding

7.2.16. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure

7.2.17. Serious, non-healing wound, active ulcer, or untreated bone fracture

7.2.18. Clear signs of tumour infiltration into the thoracic great vessels (on imaging)

7.2.19. Clear signs of cavitation of pulmonary lesions (on imaging)

7.2.20. Known history of severe allergic reactions to any platinum-containing compounds or any component of pemetrexed, bevacizumab or atezolizumab.

7.2.21. Grade ≥2 peripheral neuropathy as defined by NCI CTCAE v5.0

7.2.22. HIV or active hepatitis B or hepatitis C

7.2.23. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol.

7.2.24. Women who are pregnant or in the period of lactation.

7.2.25. Sexually active men and women of childbearing potential who are not willing to use an effective contraceptive method during the trial and up to 6 months after discontinuing protocol treatment (see Section 9.7 for effective contraceptive methods).

7.2.26. Active autoimmune disease that has required systemic treatment in past 2 years

7.2.27. History of active diverticulitis

7.2.28. Previous treatment with atezolizumab and/or bevacizumab or parallel participation in other interventional clinical trial with atezolizumab and/or bevacizumab.

8. Method of treatment assignment

This is a randomised, open-label trial. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the trial site will obtain the Patient's Identification (ID) number and treatment assignment through the randomisation system, which is integrated in the web-based electronic data capture (EDC) system ETOPdata.

Patients will be randomly assigned (1:1) to one of two treatment arms: chemotherapy and bevacizumab (control arm) or chemotherapy and bevacizumab plus atezolizumab (experimental arm). Block stratified randomisation will be performed centrally and will be balanced by institution. The stratification factors are:

- Pure epithelioid versus not
- Stage IV (according to 8th TNM classification) versus others

Patients and investigators will be unmasked to the protocol treatment assignment.

9. Protocol treatment and other treatments relevant to the trial

Atezolizumab and bevacizumab are the investigational medicinal products (IMPs) in this trial and will be supplied.

Carboplatin plus pemetrexed is the approved standard chemotherapy regimen in the first-line setting for MPM and will be sourced locally.

Complete details of the drug logistics, distribution, packaging, labelling, storage and handling as well as accountability and destruction are described in the ***BEAT-meso Drug Supply Manual***. This document is available for reference by the pharmacist and trial personnel.

9.1. Overview protocol treatment

Control arm:

- 4-6 cycles chemotherapy:
  Carboplatin AUC 5 + pemetrexed 500 mg/m^2, D1Q3W
  plus
- Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity

Experimental arm:

- 4-6 cycles chemotherapy:
  Carboplatin AUC 5 + pemetrexed 500 mg/m2, D1Q3W
  plus
- Bevacizumab 15mg/kg D1Q3W until PD, refusal or unacceptable toxicity
  plus
- Atezolizumab 1200 mg D1Q3W until PD, refusal or unacceptable toxicity

The protocol treatment for both arms should begin on the day of randomisation or as close as possible to this date (preferably within 7 days after randomisation).

9.2. Atezolizumab

Patients in the experimental arm will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (±3 days) cycle, until progression of disease determined according to the mRECIST v1.1 or lack of tolerability, or patient declines further treatment.

Please refer to the ***Atezolizumab Investigator's Brochure (IB)*** for details on nonclinical and clinical studies.

Supplies will be provided by F. Hoffmann-La Roche Ltd. For details please refer to the ***BEAT-meso Drug Supply Manual***.

9.2.1. Packaging and labelling

Supplies will be affixed with a clinical trial label in accordance with regulatory requirements.

9.2.2. Supplies disclosure

This trial is open-label; therefore, the patient, the trial site personnel, and personnel at the ETOP coordinating office are not blinded to treatment. Drug identity (name, strength) is included in the label text.

9.2.3. Storage and handling

Supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Supplies must be stored in the original container. The Principal Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. See the ***BEAT-meso Drug Supply Manual*** for complete details.

9.3. Bevacizumab

9.3.1. Administration

Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (±3 days) cycle, until progression of disease determined according to the mRECIST v1.1 or lack of tolerability, or patient declines further treatment.

9.3.2. Packaging and labelling

Supplies will be affixed with a clinical trial label in accordance with regulatory requirements.

9.3.3. Storage and handling

Supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Supplies must be stored in the original container. The Principal Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. See the ***BEAT-meso Drug Supply Manual*** for complete details.

9.4. Chemotherapy

The combination of platinum (carboplatin) combined with pemetrexed is the standard chemotherapy regimen in the first-line setting for MPM.

Patients in both treatment arms will receive carboplatin (AUC 5) plus pemetrexed (500 mg/m^2) on day one of every 3-week (±3 days) cycle for 4-6 cycles.

For additional details regarding dispensing or reconstitution, preparation of the infusion fluid, and administration for each of the standard of care chemotherapy regimens, please refer to the approved product labels and local policies for carboplatin and pemetrexed.

<u>Please note</u> that premedication with folic acid and vitamin B12 must be given according to the pemetrexed SPC.

9.4.1. Dose modification and delay criteria for carboplatin and pemetrexed

Dose modification, reductions and holds for carboplatin and pemetrexed should be performed according to local practice. Please refer to approved product labels for patients receiving these regimens.

9.5. Treatment of pleural effusion

Puncture of the thoracic effusion and installation of a tunnelled drainage catheter are allowed whenever clinically indicated. Talc- or fibrin pleurodesis are not allowed during protocol treatment. Further surgical interventions for the treatment of mesothelioma, including pleurectomy decortication or pleuro-pneumonectomy, are not allowed during protocol treatment.

In case of a local infection and especially in case of an abscess, local treatment including decortication of the abscess is allowed. However, the patient is not allowed to commence or continue protocol treatment until a complete resolution of the infection is documented.

9.6. Concomitant therapy

Concomitant medication/therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment. The use of concomitant medication/therapy judged by the investigator to be necessary for the care of the patient is permitted. The investigator should instruct the patient to notify the trial site about any new medications he/she takes after the start of the protocol treatment (also refer to Prohibited therapies in Section 9.6.1).

Concomitant medications need to be recorded as follows:

At baseline: medications or treatments for comorbidities that are used by a patient within 14 days prior to randomisation should be recorded on the ***Concomitant Medication eCRF***.

During protocol treatment: in case of an AE or SAE, all concomitant medications used to treat the event must be reported.

9.6.1. Prohibited therapies

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

- Concomitant therapy intended for the treatment of cancer, other than the treatment specified in this protocol, is prohibited during protocol treatment, until documented disease progression and the patient has discontinued protocol treatment. Prohibited concomitant therapies include, but are not limited to, chemotherapy (other than carboplatin and pemetrexed), immunotherapy (other than atezolizumab), radiotherapy, and herbal therapy, whether health authority-approved or experimental.

  Note: Palliative doses of radiation therapy and Stereotactic Body Radiation Therapy (SBRT) to a symptomatic solitary lesion or to the brain is allowed.

- Live vaccines within 4 weeks prior to the first dose of protocol treatment, while on protocol treatment and for 5 months after the last dose of protocol treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic immune stimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of protocol treatment and during protocol treatment because these agents could potentially increase the risk for autoimmune conditions **when given in combination with atezolizumab**.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during protocol treatment because these agents could potentially alter the efficacy and safety of **atezolizumab**.

9.7. Highly effective contraception methods

Women of childbearing potential and sexually active men must use highly effective contraception (methods that result in a failure rate of <1% per year) from the start of protocol treatment until at least6 months after the last dose. Examples of highly effective contraceptive methods with a failure rate of <1% per year include:

- bilateral tubal ligation
- male sterilisation (vasectomy)
- hormonal contraceptives that inhibit ovulation
- hormone-releasing intrauterine devices and copper intrauterine device

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

Patients should be informed that taking the protocol medication may involve unknown risks to the foetus if pregnancy were to occur during the trial. In order to participate in the trial they must adhere to the contraception requirement (described above) for the duration of the trial up to at least 6 months after the last dose of any protocol treatment. If there is any doubt whether a patient will reliably comply with the requirements for contraception, that patient should not be entered into the trial.

9.8. Treatment duration

Patients remain on treatment until one of the following events, whichever occurs first:

- Documented progression according to the mRECIST v1.1
- Unacceptable toxicity to protocol treatment
- Medical condition that prevents further treatment
- Patient withdraws consent
- Patient becomes pregnant

10. Tumour response evaluation

All included patients will be evaluated for disease response and progression by the investigator according to the updated modified RECIST criteria for the assessment of response in mesothelioma version 1.1 (mRECIST v1.1).[29]

10.1. Modified RECIST for assessment of response in malignant pleural mesothelioma version 1.1 (mRECIST v1.1)

The updated modified RECIST for mesothelioma version 1.1 explicitly formalizes the "measurement site" concept for image-based mesothelioma tumour assessment. Measurements of tumour thickness (constructed perpendicular to a tangent to the curve of the pleura at the outer tumour margin measurement endpoint) acquired from these measurement sites form the basis for mesothelioma tumour response assessment.

In this trial patients must have measurable or evaluable (non-measurable) disease (see definitions below).

10.1.1. Definition of measurability:

- Pleural tumour is measurable if there exists at least one pleural site for which tumour thickness is ≥7 mm.
- Non-pleural sites of disease can determine measurability, and will have a unidimensional greatest diameter of ≥10 mm at baseline.
- Measurable involved lymph nodes have a short-axis measurement ≥15 mm at baseline.
- Pleural effusion is not considered a measurable lesion.

10.1.2. Measurement requirements:

- mRECIST v1.1 specifies selection of up to 6 pleural measurement sites at baseline (with no more than 2 sites per CT section and sites selected across no more than 3 sections each separated by at least 1 cm); each site must satisfy the criterion for minimally measurable disease.

- If baseline scan measurement line segments are viewed when acquiring measurements from follow-up scans, the preferred association of measurement sites with anatomic landmarks can be relaxed. Consideration of sites that "lend themselves to reproducible repeated measurements" should be maintained.
- Only measurement sites selected at baseline are to be included in the summed tumour measurements on subsequent CT scans.
- Measurement on axial CT sections displayed with a soft-tissue window is strongly preferred.
- Measurement sites located (1) superior to the level of the left atrium and (2) below the level of the aortic arch are preferred.
- Pleural effusion should never be included in the measurement of tumour thickness.
- The pleura in both hemithoraces is considered a single "organ" if bilateral disease is present so that the up-to-6 pleural measurement sites may be distributed across both hemithoraces; while no more than 2 sites may be selected in any one CT section for any one hemithorax, section selection is to be considered for each hemithorax independently.

10.1.3. Measurement process:

- mRECIST v1.1 recommends that the same observer acquire measurements from all CT scans from a given patient using the same image display parameters (e.g., contrast/brightness settings).

  Please note: Observers acquiring measurements for mesothelioma should be familiar with mRECIST v1.1 guidelines, should be experienced with measurement site selection and visual considerations for constructing measurements, and should be trained to use the software tool being implemented locally to acquire those measurements.
- mRECIST v1.1 recommends that images of the baseline scan measurement line segments be stored and visually referenced when acquiring measurements from scans at subsequent time points.
- Once a baseline tumour thickness measurement has been acquired at a measurement site, all subsequent measurements of that measurement site across time points should be oriented in the same direction as the baseline scan measurement.
- If chest wall and mediastinal relationships have altered such that two measurement sites on a baseline scan section are not seen on the same section of a follow-up scan, subsequent measurements should use the section(s) that best corresponds with each baseline measurement site.

- mRECIST v1.1 recommends follow-up measurement of all sites that reduce in size below the minimum measurable size, if such a measurement can be obtained, and a default value of 2 mm if tumour is present at a site but is too thin to measure.

10.1.4. Non-pleural lesions:

- "Measurable" non-pleural lesions require acquisition of longest-diameter measurements (10-mm minimum) from "a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs." Pleural site measurements are considered a contribution from one organ; the number of measurements attributed to the pleura for this accounting will not exceed two (even if 6 are selected).
- All measurements (pleural and non-pleural) are summed to acquire a single summed measurement.

10.1.5. Lymph nodes, non-measurable pleural disease, measurable but non-measured pleural disease, and new lesions or foci of pleural thickening:

- mRECIST v1.1 includes lymph nodes in the summed measurement, when appropriate, subject to the standard RECIST v1.1 accounting of measurements.
    - Measurable malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan, assuming the slice thickness ≤5 mm. At baseline and in follow-up, only the short axis will be measured.
    - Non-measurable malignant lymph nodes: Small lymph nodes (short axis ≥10 and <15 mm). Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed as measurable or non-measurable disease.
- Pleural disease (1) measurable but not utilized as a measurement site or (2) considered to be "non-measurable" should be characterized by descriptive notations. Non-measurable pleural disease and measurable but non-measured pleural disease may be incorporated into the same descriptive notation.
- Under mRECIST v1.1, an unequivocal new non-pleural lesion or an unequivocal new focus of pleural thickening that exceeds the minimum measurable size would be considered progressive disease.

10.2. Selection of target lesions

The total tumour measurement is the sum of all pleural tumour thickness measurements at baseline plus the unidimensional measurements based on the standard RECIST method (RECIST v1.1).

A maximum of five target lesions in total (and a maximum of two lesions per organ) representative of all involved lesions, can be selected. Pleural site measurements are

considered a contribution from one organ. The number of measurements attributed to the pleura for consistency with the standard RECIST 1.1 accounting will not exceed two, even if 6 pleural sites are selected.

Note: pleural effusions are considered non-measurable disease.

10.2.1. Measurement sites at baseline

- Unidimensional pleural tumour measurements should be determined by constructing a line segment perpendicular to a tangent to the curve of the pleura at the outer measurement point (illustrated in Figure 1 of Appendix 2). The outer measurement point is best placed on the chest wall or mediastinum, avoiding the anterior pleural reflexion.
- Image sections chosen for measurement should be readily identified at subsequent time points and ideally related to clear fixed anatomical mediastinal or chest wall landmarks (illustrated in Figure 2 of Appendix 2).
- Areas of pulmonary atelectasis, pleural effusion, and indistinct tumour boundaries should be avoided if possible.
- Where a measurement site is related to the pulmonary fissures, unidimensional measurements should be made perpendicular to a tangent to the pleura at that point (illustrated in Figure 3 of Appendix 2).
- Pleural thickness is recorded at up to two measurement sites, if possible, at each of up to three separate axial sections (levels) of the thoracic CT scan at baseline (illustrated in Figures 2 and 4 of Appendix 2). Axial sections should be at least 1 cm apart. The sum of these (up to) 6 measurements gives the baseline sum of pleural measurements.
- Each selected measurement must individually satisfy the criterion for minimally measurable disease (see Section 10.1.1).
- In the event of bilateral disease, the pleura is considered a single organ and pleural measurement sites may be distributed across both hemithoraces, up to three independent CT sections per hemithorax, no more than two measurement sites per section, to a total of 6 sites.
- Additional unidimensional non-pleural target lesion measurements meeting the definition of measurable disease may be made of involved lymph node sites, chest wall masses, or metastatic disease and added to the sum of pleural tumour thickness measurements to give a baseline sum of target lesion measurements.
- Measurements of non-pleural disease (according to the standard RECIST v1.1[30]) may be included from a maximum of 5 lesions in total, and a maximum of 2 lesions per organ. Measurements acquired from pleural sites are to be considered a contribution from one organ.

- Other disease present at baseline should be recorded as “non-target lesions.” In the case of diffuse pleural disease, examples of descriptive notations include:
    - “extensive pleural thickening”
    - “circumferential pleural thickening”
    - “tumour indistinguishable from diaphragm in base,”
    - “extensive pleural nodularity” or similar.

  This may include non-measureable disease as well as measurable but non-measured pleural disease. It is not practical to separately identify individual pleural lesions that are contiguous or exceed a reasonable number.
- Images of the baseline scan measurement segments should be stored for visual reference when measuring subsequent images.

10.2.2. Measurement of disease at subsequent time points:

- Pleural tumour measurements should always be performed at the same site, in the same orientation (direction), and with the same image display parameters as the baseline measurement, irrespective of changes in lesion morphology and shape. If tumour is present at a site but is too thin to measure on a magnified window, a default value of 2 mm should be used.
- Lesions that are viewed on the same image slice at baseline but are subsequently best viewed on different images slices due to alterations in thoracic contraction, respiration, or patient positioning may be measured on different slices on subsequent scans.
- It is recommended that the same observer acquire measurements from all CT scans from a given patient.
- Stored images of the baseline measurement line segments should be visually referenced when acquiring measurements from scans at subsequent time points.

10.3. Non-measurable (evaluable) disease

Non-measurable disease is defined as lesions or sites of disease that cannot be measured.

10.3.1. Non-measurable lesions/sites of disease and special considerations:

- Small non-nodal lesions (longest diameter <10 mm in CT scan)
- Small lymph nodes (short axis ≥10 and <15 mm). Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed as measurable or non-measurable disease.
- Bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue

component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Lymphangitic involvement of skin or lung
- Cystic lesions. Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions
- Tumour lesions situated in a previously irradiated area, or subjected to other loco regional therapy. Such lesions may be considered measurable if there has been demonstrated progression in the lesion
- Abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

10.3.2. Selection of non-target lesions

Non-target lesions should be identified. All other lesions (or sites of disease) not identified as target lesions should also be recorded as non-target lesions at baseline.

Note: pleural effusion is a non-target lesion.

For non-target lesions, measurements are not required, but the presence or absence of each lesion should be noted throughout follow-up. It is possible to record multiple non-target lesions as a single item on the eCRF (e.g. "multiple liver metastases").

10.4. Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumour effect of a treatment.

CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. CT scan should generally be performed using a ≤5 mm contiguous reconstruction algorithm. Magnetic Resonance Imaging (MRI) is acceptable for certain situations, e.g. body scans.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules) and ≥10 mm. In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable. Ultrasound is not useful in assessment of lesion size and is not accepted as a method of assessment.

FDG-PET is not recommended for response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a PET/CT scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT scan performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT scan (with i.v. and oral contrast), then the CT scan portion of the PET/CT can be used for RECIST measurements.

10.5. Definitions of response

10.5.1. Target lesions

Complete response (CR)

The disappearance of all pleural and non-pleural disease (including pleural thickening considered to represent tumour) with no evidence of tumour elsewhere. Lymph nodes selected as target lesions must each have reduction in the short axis to <10 mm in order for the response to be considered complete. In this case, the sum of diameters may be >0.

Partial response (PR)

Summed measurement decrease by at least 30% from the baseline scan summed measurement, which must be confirmed at a subsequent follow-up scan at least 4 weeks later (at which time the summed measurement must not exceed 70% of the baseline scan summed measurement).

Stable disease (SD)

A decrease in the summed measurement that does not qualify as PR, or an increase in the summed measurement that does not qualify as PD.

Progressive disease (PD)

Summed measurement increase by at least 20% from the nadir of the summed measurements from all prior scans (up to and including the baseline scan), even if the summed measurement is ≤70% of the baseline scan summed measurement; classification as PD also requires an absolute summed measurement increase of at least 5 mm over the nadir summed measurement.

An unequivocal new non-pleural lesion or an unequivocal new focus of pleural thickening that exceeds the minimum measurable size (and represents either a pleural tumour mass physically distinct from that associated with existing measurement sites or a region of a previously existing pleural tumour mass that would now unequivocally qualify as a measurement site) would be considered progressive disease. The assessment of

"unequivocal," however, requires judgment and careful review to ensure that the lesion was not present previously in an adjacent section.

10.5.2. Non-target lesions (evaluable disease)

Complete Response (CR)

Disappearance of all non-target lesions; lymph nodes selected as non-target lesions must be non-pathological in size (<10 mm).

Non-CR/non-PD

Persistence of one or more non-target lesions (non-CR).

Progressive disease (PD)

The appearance of new lesions and/or the unequivocal progression of existing non-target lesions. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease or an overall substantial increase in tumour burden that merits treatment discontinuation.

Note: Deterioration of pleural effusion is not necessarily regarded as PD in the absence of other clinical features consistent with PD. Clinical interpretation of deterioration of pleural effusion is required. Deteriorating pleural effusion can be managed through local intervention like thoracentesis as clinically appropriate.

10.6. Determination of new lesions

The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique or findings thought to represent something other than tumour).

If a new lesion is equivocal, (e.g., because of its small size) the decision on PD cannot be based on this lesion only.

Lesions or sites of disease found in a new location not included in the baseline scan (e.g., brain metastases) are considered new lesions.

Note: The "re-appearance" of a previously "disappeared" target or non-target lesion is not to be considered as new lesion and does not in itself qualify as PD unless the overall evaluation meets the PD criteria or the patient was previously in CR.

10.7. Determination of overall response

Based on the responses of target lesions, non-target lesions, and the presence or absence of new lesions, the overall response will be determined at each tumour evaluation time point, according to Table 1 (for patients with measurable disease) and Table 2 (for patient with non-measurable disease) below.

For patients with measurable disease

Table 1: Overall response for measurable disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR / non-PD*	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

For patients with non-measurable disease

Table 2: Overall response for non-measurable disease

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR / non-PD*	No	Non-CR / non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

*Non-CR/non-PD should be used rather than SD for categorizing non-target lesions.

10.8. CT schedule for response evaluation

Radiological tumour assessment by contrast enhanced CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included, preferred) or alternatively (and only after the first CT at baseline) contrast enhanced CT of thorax and ultrasonography of upper abdomen following the schedule indicated below; until tumour progression determined according to the mRECIST v1.1. The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial.

At baseline:	within 5 weeks before randomisation
After randomisation:	every 6 weeks* (42 days), e.g., at week 6, 12, 18, 24 … (±4 days) until progression.

* From start of protocol treatment

10.9. Storage of images for central review

All CT images must be stored locally in electronic format for later central review, please consult the ***BEAT-meso Procedures Manual*** for details.

Any information from which the identity of patients could be deduced must be removed before transferring any imaging data for central review (e.g. initials, birth date etc.).

11. Trial procedures

This section provides details about procedures, clinical and laboratory evaluations and follow-up investigations at individual visits.

11.1. Tumour assessment

Radiological tumour assessment by contrast enhanced CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) will be done as indicated in Section 10.8 until progression of disease.

11.2. Baseline evaluations

The following evaluations should be done within 5 weeks before randomisation.

Written informed consent:

Before any trial specific evaluations or interventions (within 6 weeks before randomisation).

11.2.1. Demographics

Year of birth, gender, race

11.2.2. Medical history

Including smoking history, asbestos exposure, employment history, medications, comorbidities, allergies and baseline symptoms (baseline symptoms will be recorded on the ***adverse events eCRF)***.

11.2.3. Vital signs:

According to local standards, including performance status, blood pressure, heart rate, and temperature, body weight and height (at baseline only).

11.2.4. Quality of life assessment (before randomisation)

11.2.5. Thyroid function

TSH, free T3 (or total T3 if free T3 is not performed per local standard), and free T4 at baseline.

11.2.6. HIV and hepatitis B and C status

11.2.7. Pregnancy test

Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum pregnancy test within 2 weeks before randomisation. Pregnancy testing has to be repeated throughout protocol trial treatment according to local standards.

11.2.8. Chemistry

Serum albumin, glucose, potassium, sodium, calcium, magnesium, amylase and lipase.

11.2.9. Haematology

Haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

11.2.10. Coagulation profile

INR

11.2.11. Liver function test

Total bilirubin, ALT, AST, ALP, GGT and LDH.

11.2.12. Renal function test

Urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault (see Section 7.1.9).

11.2.13. Urine analysis

On first morning urine sample: pH, specific gravity, glucose, protein, ketones and blood, dipstick permitted. Patients with urine dipstick reading for protein 2+ or higher should undergo further assessment with a 24-hour urine collection. Treatment cycle may only be administered if result is <2g/24 hours.

11.2.14. Radiological tumour assessment

By contrast enhanced CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included), performed within 5 weeks before randomisation.

11.2.15. TNM categories (according to the 8th TNM classification)

Pathology report

A copy of the pathology report (from the diagnostic biopsy at baseline) should be uploaded in ETOPdata (all information allowing identification of the patient, e.g., patient's name, day and month of birth, must be removed and the ETOP patient identification number added)

11.2.16. FFPE tumour material for translational research

FFPE tumour material from a biopsy sample, taken prior to protocol treatment start must be submitted, either from archival tumour or from a fresh biopsy taken >7 days prior to protocol treatment start.

11.2.17. Blood samples for translational research (see Section 12.2.2 details):

- 2.5 mL whole blood for RNA analysis
- 2.5 mL whole blood for DNA analysis
- Serum samples from 5 mL blood.

11.3. Evaluations in the control arm

At each treatment cycle:

The following evaluations have to be done at every treatment cycle, within 3 days before treatment administration:

11.3.2. Vital signs

According to local standards, including performance status, blood pressure, heart rate, temperature and body weight.

11.3.3. Recording of adverse events

11.3.4. Chemistry

Serum albumin, glucose, potassium, sodium, calcium, magnesium, amylase and lipase.

11.3.5. Haematology

Haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

11.3.6. Liver function test

Total bilirubin, ALT, AST, ALP, GGT and LDH.

11.3.7. Renal function test

Urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault (see Section 7.1.9).

11.3.8. Quality of life assessment

Within 3 days before treatment administration in cycles 2-5 (e.g., at weeks 3, 6, 9 and 12) and cycles 7 and 9 (e.g., at weeks 18 and 24) **OR** until end of protocol treatment, whatever is first.

Every 2nd treatment cycle

The following evaluations have to be done within 3 days before the administration of every 2nd treatment cycles:

11.3.9. Coagulation profile

INR

11.3.10. Urine analysis

On first morning urine sample: pH, specific gravity, glucose, protein, ketones and blood, dipstick permitted. For as long as the patient is receiving bevacizumab, for urine dipstick reading for protein 2+ or higher, patient should undergo further assessment with a 24-hour urine collection. The next cycle of bevacizumab may only be administered if result is <2g/24 hours.

At treatment cycle 3

The following additional evaluation has to be done at cycle 3, within 3 days before treatment administration:

11.3.11. Blood sample for translational research (see Section 12.2.2 details):

- 2.5 mL whole blood for RNA analysis
- Serum samples from 5 mL blood.

11.4. Evaluations in the experimental arm

At each treatment cycle:

The following evaluations have to be done at each cycle, within 3 days before treatment administration:

11.4.2. Vital signs

According to local standards, including performance status, blood pressure, heart rate, temperature and body weight.

11.4.3. Recording of adverse events

11.4.4. Chemistry

Serum albumin, glucose, potassium, sodium, calcium, magnesium, amylase and lipase.

11.4.5. Haematology

Haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

11.4.6. Liver function test

Total bilirubin, ALT, AST, ALP, GGT and LDH.

11.4.7. Renal function test

Urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault (see Section 7.1.9).

11.4.8. Quality of life assessment

Within 3 days before treatment administration in cycles 2-5 (e.g., at weeks 3, 6, 9 and 12) and cycles 7 and 9 (e.g., at weeks 18 and 24) **OR** until end of protocol treatment, whatever is first.

Every 2nd treatment cycle

The following evaluations have to be done at every 2nd cycle, within 3 days before treatment administration:

11.4.9. Coagulation profile

INR

11.4.10. Urine analysis

On first morning urine sample: pH, specific gravity, glucose, protein, ketones and blood, dipstick permitted. For as long as the patient is receiving bevacizumab, for urine dipstick reading for protein 2+ or higher, patient should undergo further assessment with a 24-hour urine collection. The next cycle of bevacizumab may only be administered if result is <2g/24 hours.

At treatment cycle 3

The following additional evaluation has to be done at cycle 3, within 3 days before treatment administration:

11.4.11. Blood sample for translational research (see Section 12.2.2 for details):

- 2.5 mL whole blood for RNA analysis
- Serum sample from 5 mL blood.

At every 4th treatment cycle

The following additional evaluation has to be done at cycle 1, within 3 days before treatment administration and then every 4th treatment cycle (i.e. cycle 1, 5, 9, 13, etc.):

11.4.12. Thyroid function

TSH, free T3 (or total T3 if free T3 is not performed per local standards), and free T4 at baseline before randomization, at cycle 1, within 3 days before treatment administration and then every 4th treatment cycle (i.e. cycle 5, 9, 13, etc.; within 3 days before treatment administration).

11.5. Evaluations at disease progression

11.5.1. FFPE: tumour re-biopsy is strongly encouraged

A copy of the pathology report from re-biopsy at progression should be uploaded in ETOPdata (all information allowing identification of the patient, e.g., patient's name, day and month of birth, must be removed and the ETOP patient identification number added).

11.5.2. Blood samples for translational research (see Section 12.2.2 for details):

- 2.5 mL whole blood for RNA analysis
- Serum sample from 5 mL blood.

11.6. Evaluations at the end of treatment visit

Patients are considered to be on protocol treatment for as long as they receive either chemotherapy, bevacizumab and/or atezolizumab. At the end of all protocol treatments and irrespective of the reason for stopping treatment, an end of treatment visit at the centre is to be scheduled within 30 days following the decision to stop trial treatment or within 30 days after planned treatment start if treatment never started. This visit has to be done for all patients, including those who did not start trial treatment. In case a new anticancer therapy is initiated within 30 days following the decision to stop trial treatment, the visit is ideally to be scheduled before the start of the new treatment.

In case treatment was delayed due to AEs and could not be resumed, the end of treatment visit should be performed within 10 weeks after the last dose. The following procedures should be performed:

11.6.1. Vital signs

According to local standards, including performance status, blood pressure, heart rate, temperature and body weight.

11.6.2. Recording of adverse events

11.6.3. Chemistry

Serum albumin, glucose, potassium, sodium, calcium, magnesium, amylase and lipase.

11.6.4. Haematology

Haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count).

11.6.5. Liver function test

Total bilirubin, ALT, AST, ALP, GGT and LDH.

11.6.6. Renal function test

Urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault (see Section 7.1.9).

11.6.7. Radiological tumour assessment has to be repeated if not done within 6 weeks prior to end of treatment visit

11.7. Evaluations in the follow-up phase (post treatment) before progression

Patients who discontinue trial treatment before progression should have the following examinations documented every 6 weeks (±4 days), aligned with the imaging visits.

11.7.1. Vital signs

According to local standards, including performance status, blood pressure, heart rate, temperature and body weight.

11.7.2. Radiological tumour assessment

By contrast enhanced CT scan of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included).

11.8. Evaluations in the follow-up phase beyond progression

Patients with progression that ends trial treatment will be followed up every 12 weeks (±3 weeks) or more frequently, if needed, starting from date of progression until trial end. They should have documented:

11.8.1. Further lines of treatment

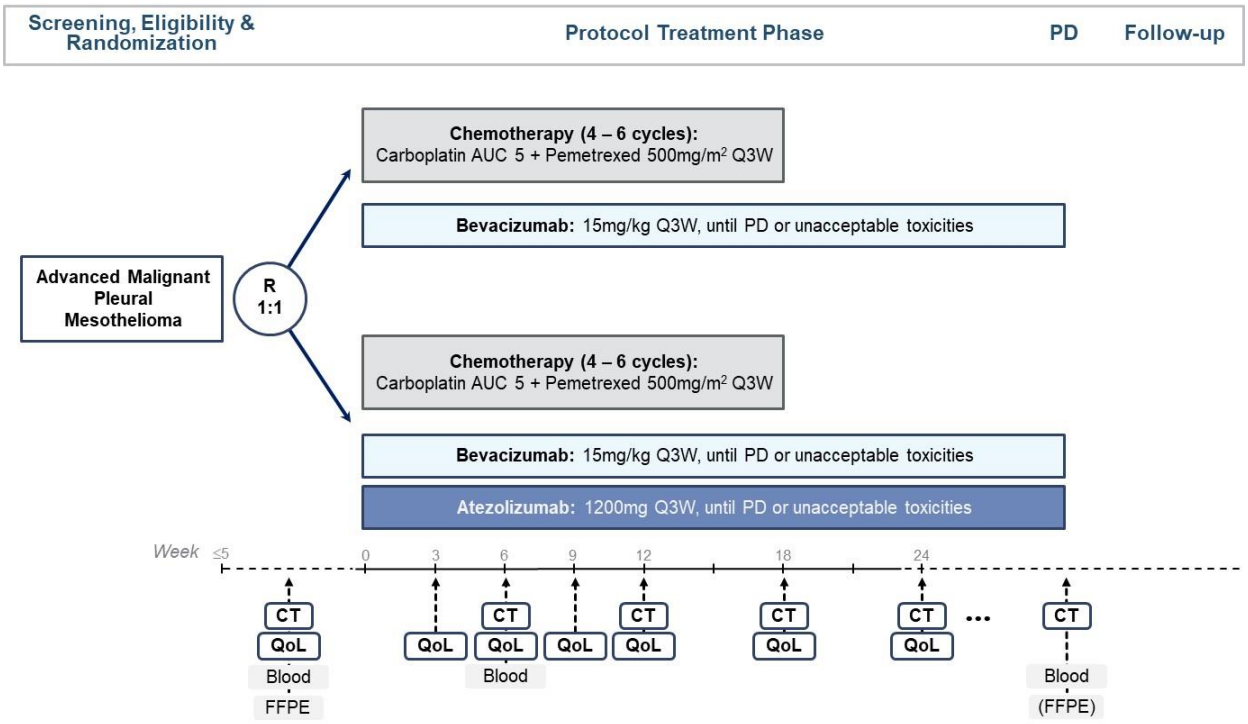
11.8.2. Survival

12. Biological material and translational research

12.1. Biobanking

A biobank for all biological material collected from every patient randomised in this trial will be established for translational research, which is integral to the trial. The required pathological material (described below) is submitted to, catalogued, and maintained at the BEAT-meso Central Laboratory, located at Center for Experimental Therapeutics CTE, CHUV Lausanne, Switzerland. Formalin-fixed, paraffin-embedded (FFPE) tumour tissue blocks (tissue blocks, resection or biopsy specimen) taken prior to protocol treatment start, along with whole blood and serum samples will be centrally collected and biobanked at the Central Laboratory in Lausanne, Switzerland.

The material will be centrally archived and will undergo central histology review and biomarker testing. Following the completion of the primary trial translational research objectives, the biological material will be made available for further translational research.



12.2. Mandatory biomaterial

12.2.1. FFPE-material

FFPE tumour tissue availability must be confirmed at the time of randomisation and the material shipped within 4 weeks thereafter.

FFPE tumour material from a biopsy sample, taken prior to protocol treatment start must be submitted, either from archival tumour or from a fresh biopsy taken >7 days prior to protocol treatment start.

- Submission of FFPE material is mandatory. An FFPE tumour tissue block is requested. Only if the block is not available, 15 slides of 4-5 µm thickness are an

acceptable alternative to the block. If slides are submitted in lieu of the block, slides must be freshly cut and shipped to the central reference laboratory within 1 week of sectioning.

- Cytological specimens are not accepted in this trial.

12.2.2. Blood and serum samples

At baseline

Baseline samples have to be taken within 5 weeks before randomization. If this is not possible, they may be taken after randomization but must be taken before the administration of the first treatment cycle.

- 2.5 mL whole blood (for DNA germline mutation assessment as a reference for tumour somatic mutation analysis)
- 2.5 mL whole blood (for RNA profiling)
- Serum samples from 5 mL blood

Within 3 days before the administration of treatment cycle 3

- 2.5 mL whole blood (for RNA profiling)
- Serum samples from 5 mL blood

At disease progression

- 2.5 mL whole blood (for RNA profiling)
- Serum samples from 5 mL blood

All blood samples should be immediately frozen at -80ºC.

12.3. Additional biomaterial

12.3.1. FFPE-material

FFPE tumour block (preferred) from re-biopsy at disease progression or alternatively 15 tissue sections of 4-5 µm thickness and, if there is sufficient material also 10 tumour tissue sections of 15 µm thickness.

Additional slides are requested, if the baseline FFPE tumour block is not already provided within the mandatory sample set (see section 12.2). An additional 10 tumour tissue sections of 15 µm thickness, either from archival tumour or fresh biopsy taken >7 days prior to protocol treatment start is are requested, if feasible.

12.4. Submission of biomaterial

All biological samples collected during the conduct of the trial must be marked with the patient identifier issued by the EDC system and registered in the system. FFPE tumour tissue

and blood samples will be shipped to the central reference laboratory in Lausanne (refer to location below).

12.5. Submission of FFPE material

- FFPE tumour material as defined in Section 12.2.1 and Section 12.3. FFPE blocks/slides must be marked with the ETOP patient identification number issued by the EDC system (all information allowing identification of the patient, e.g.; patient name, day and month of birth, must be removed).
- Pathology report from the diagnostic biopsy, either from archival tumour or from a fresh biopsy taken > 7days prior to protocol treatment start (all information allowing identification of the patient, e.g., patient's name, day and month of birth, must be removed and the ETOP patient identification number added).
- Pathology report from re-biopsy at progression (all information allowing identification of the patient, e.g., patient's name, day and month of birth, must be removed and the ETOP patient identification number added).

Tumour material should be submitted as soon as obtained (but not no later than 4 weeks after patient randomisation), and documented in the **Biological Material Tracking eCRF** in the EDC system. On request, blocks can be returned to the submitting site within a reasonable time frame (est. 3 months) after slides for the planned analyses have been cut.

Please ensure that the blocks and/or slides are carefully packaged according to the ***BEAT-meso Procedures Manual***, as otherwise they could easily get damaged during transport.

Samples have to be sent to:

CHUV - Department of Oncology
Center for Experimental Therapeutics (CTE)
Hôpital Orthopédique, HO 05/1552
Av. Pierre-Decker 4
CH-1011 Lausanne, Switzerland

12.6. Submission of blood samples

For blood collection and serum preparation see ***BEAT-meso Procedures Manual***.

Blood samples as defined in Section 12.2.2 and Section 12.3.

Blood samples must be stored locally at -80ºC and will be kept at the participating site until shipment. Shipments will be arranged centrally.

12.7. Translational research

The biological material collected during the trial and the associated translational research projects under consideration are listed in Table 3. These projects will be continuously adapted according to growing knowledge about immunological modification and potential biomarkers of immune checkpoint inhibitor therapy. Translational research studies will be conducted by ETOP-internal and -external collaborators in line with the ETOP iBiobank policy.

Table 3: Overview of planned translational research studies

Sample	Time point			Potential analyses
	Baseline*	Cycle 3**	PD	
FFPE (To be shipped to the central laboratory within 4 weeks after randomisation) **Slides** (freshly cut and shipped to the central laboratory within 1 week after sectioning)				
Tumour block **OR** min. 15 sections of 4-5 µm	Mandatory		Strongly recommended	- Tumour Mutational Burden - PD-L1 (IHC) - PD-L2 (IHC)
10 sections of 15 µm	Strongly recommended		Strongly recommended	- DNA/RNA (NGS)
Archival tumour material from primary diagnosis must be submitted. (A fresh FFPE biopsy sample taken >7 days prior to protocol treatment start is **mandatory** if the archival tumour material is fully depleted).				
Blood samples (Frozen samples kept at site at -80°C until the shipment is centrally arranged at the end of study.)				
Whole blood – RNA	2.5 mL	2.5 mL	2.5 mL	- RNA profiling
Whole blood – DNA	2.5 mL			- Germline mutation reference (HLA haplotype)
Serum	5 mL	5 mL	5 mL	- Cytokines - ctDNA - IL-6 - Mesothelin - CRP
* Taken within 5 weeks before randomization. If this is not possible, they may be taken after randomization but must be taken before the administration of the first treatment cycle ** Taken within 3 days before the administration of treatment cycle 3				

13. Criteria for termination of the trial

13.1. General criteria for termination of the trial

The trial may be discontinued early in part or completely if information gained about the protocol treatment leads to doubt as to the benefit/risk ratio, by decision of the ETOP Foundation Council upon recommendation of the ETOP 13-18 BEAT-meso Steering Committee. Specific considerations will be based on the regular safety reviews by the ETOP Independent Data Monitoring committee (IDMC).

The trial can be terminated at any time if the authorization and approval to conduct the trial is withdrawn by an ethics committee or regulatory authority decision, or due to insufficient accrual, or if emerging new data impacts the scientific value of the trial or on ethical grounds.

13.2. Discontinuation of protocol treatment for individual patients

Protocol treatment should be stopped in the following situations:

- Disease progression according to the mRECIST v1.1.
- Occurrence of unacceptable toxicities. Stopping protocol treatment is determined by medical judgment of the treating physician.
- Request by the patient. Patients have the right to refuse further protocol treatment at any time during the trial. Such patients will remain in the trial and will be transferred to the follow-up phase.
- If a patient refuses to have the treatments or follow-up examinations and tests needed to determine whether the treatment is safe and effective.

The decision for discontinuation of protocol treatment of individual patients is taken by the treating physician based on her/his medical evaluation and taking into account the patient's individual situation.

13.3. Withdrawal of consent

Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. The data recorded up to the time point of withdrawal will remain coded and will continue to be evaluated in the trial. The investigator should ask the patient for consent to continue to collect information on her/his disease and survival status.

It should be documented in both the medical records and in the eCRF, according to the instructions in the ***BEAT-meso CRF Completion Guidelines***, if the patient accepts to be contacted for survival status or to retrieve this information from public information source (e.g., county records), despite withdrawing trial consent . For the patient's safety, an end of treatment visit should be performed and documented in the eCRF if the patient agrees to this.

ASSESSMENTS OF SAFETY

14. Safety plan

Clinical experience with atezolizumab and bevacizumab are described in the most recent versions of the Investigator's Brochure for each IMP.

The safety plan for patients in the BEAT-meso trial is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 14.1 and Section 14.2).

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the trial. Administration of atezolizumab and bevacizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation of atezolizumab are provided in Section 14.1.1 and Section 14.1.2 and for bevacizumab in Section 14.2.4 and 14.2.5.

14.1. Risks associated with atezolizumab

Atezolizumab has been associated with risks such as infusion-related reactions and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, myositis, and severe cutaneous adverse reactions. Please refer to Section 14.1.2 for the management of atezolizumab related toxicities.

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic aetiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered after consultation with ETOP Medical Affairs (medical.affairs@ibcsg.org) if the patient is deriving benefit and has fully recovered from the immune-mediated event.

14.1.1. Dose modification and treatment interruptions for atezolizumab.

There will be no dose modifications for atezolizumab in this trial. In patients experiencing toxicity, atezolizumab treatment may be temporarily suspended as described below:

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to atezolizumab treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >105 days after event onset, the patient will be discontinued from atezolizumab.

Exception: Atezolizumab may be withheld for >105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >105 days if ETOP Medical Affairs agrees that the patient is likely to derive clinical benefit.

Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with approval from ETOP Medical Affair. The investigator and the ETOP Medical Affair will determine the acceptable length of treatment interruption.

14.1.2. Management guidelines of atezolizumab related toxicities

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic aetiology, when clinically indicated.

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit-risk balance for a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only if ETOP Medical Affairs agrees that the patient is likely to derive clinical benefit.

Guidelines for managing patients who experience selected adverse events are provided in the following sections.

Pulmonary events

Dyspnoea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the trial at every tumour assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Please see Table 4 for the management guidelines for pulmonary events.

Table 4: Management guidelines for pulmonary events, including pneumonitis

Event	Management
Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • For recurrent events, treat as a grade 3 or 4 event.
Grade 3 or 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Bronchoscopy or bronchoscopic alveolar lavage is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout protocol treatment. Management guidelines for hepatic events are provided in Table 5.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests performed immediately and reviewed before administration of the next atezolizumab dose.

For patients with elevated liver function tests, concurrent medication, viral hepatitis, and toxic or neoplastic aetiologies should be considered and addressed, as appropriate.

Table 5: Management guidelines for hepatic events

Event	Management
Grade 1	Continue atezolizumab. Monitor liver function tests until values resolve to within normal limits or to baseline values.
Grade 2	**All events:** Monitor liver function tests more frequently until return to baseline values. **Events of >5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to grade 1 or better, resume atezolizumab. [b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish aetiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhoea or colitis are provided in Table 6.

All events of diarrhoea or colitis should be thoroughly evaluated for other more common aetiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandaemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 6: Management guidelines for gastrointestinal events (diarrhoea or colitis)

Event	Management
Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month

Event	Management

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Endocrine events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 7.

Patients with unexplained symptoms such as headache, fatigue, myalgia, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone (ACTH) levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 7: Management guidelines for endocrine events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.

Event	Management
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Symptomatic adrenal insufficiency	
Grade 2-4	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1- 2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.[b] • If event does not resolve to grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Hyperglycaemia	
Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism)	
Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • For recurrent hypophysitis, treat as a grade 4 event.

Event	Management
Grade 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement therapy if clinically indicated.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Ocular events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 8.

Table 8: Management guidelines for ocular events

Event	Management
Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a grade 2 event.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Refer patient to ophthalmologist. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.

Event	Management

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Immune-mediated myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnoea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 9.

Table 9: Management guidelines for immune-mediated myocarditis

Event	Management
Grade 1	• Continue atezolizumab.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset[a] contact ETOP Medical Affairs. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation, or ventricular assist device as appropriate. • Consider treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]

Event	Management
Grade 3-4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation, or ventricular assist device as appropriate. • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over≥1 month.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Infusion-related reactions and cytokine-release syndrome

No premedication is indicated for the administration of cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction with cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., paracetamol) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated infusion-related reaction because of its potential for causing agranulocytosis.

Infusion-related reactions are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

Cytokine-release syndrome is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T-cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction.[31] Cytokine-release syndrome has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019),[32-34] including atezolizumab.

There may be significant overlap in signs and symptoms of infusion-related reaction and cytokine-release syndrome, and in recognition of the challenges in clinically distinguishing

between the two, consolidated guidelines for medical management of infusion-related reactions and cytokine-release syndrome are provided in Table 10.

Table 10: Management guidelines for infusion-related reactions and cytokine-release syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged cytokine-release syndrome (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for infusion-related reactions and cytokine-release syndrome.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the intensive care unit, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic cytokine-release syndrome (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the intensive care unit is recommended), permanently discontinue atezolizumab, and contact the ETOP Medical Affairs. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for infusion-related reactions and/or cytokine-release syndrome. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the ETOP Medical Affairs.

Event	Management
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab and contact the ETOP Medical Affairs.[f] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. Monitor cardiopulmonary and other organ function closely; monitoring in the intensive care unit is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic cytokine-release syndrome (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to intensive care unit and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the ETOP Medical Affairs.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact the ETOP Medical Affairs.[f] • Administer symptomatic treatment.[c] • Admit patient to intensive care unit and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic cytokine-release syndrome (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator and in consultation with the ETOP Medical Affairs. • Hospitalize patient until complete resolution of symptoms.

Event	Management

a. Grading system for management guidelines is based on ASTCT consensus grading for cytokine-release syndrome. CTCAE v5 should be used when reporting severity of infusion-related reactions, cytokine-release syndrome, or organ toxicities associated with cytokine-release syndrome on the ***Adverse Events eCRF***. Organ toxicities associated with cytokine-release syndrome should not influence overall cytokine-release syndrome grading.

b. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop cytokine-release syndrome and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

d. Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

e. There are case reports where anti-cytokine therapy has been used for treatment of cytokine-release syndrome with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event.[32-34]

f. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for infusion-related reactions and/or cytokine-release syndrome. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the ETOP Medical Affairs and considering the benefit-risk ratio. Refer to Riegler et al. (2019) for information on experimental treatments for cytokine-release syndrome.[35]

Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)

Immune-mediated reactions may involve any organ system and may lead to haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014).[36] A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
    - Haemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
    - Platelet count <100× 10^9/L (100,000/μL)
    - ANC <1.0× 10^9/L (1000/μL)
- Fasting triglycerides >2.992 mmol/L (265mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Haemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016).[37] A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
    - Platelet count ≤181× 10^9/L (181'000/μL)
    - AST ≥48 U/L
    - Triglycerides >1.761 mmol/L (156 mg/dL)
    - Fibrinogen ≤3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 11.

Table 11: Management Guidelines for Suspected HLH or MAS

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs (medical.affairs@ibcsg.org). • Consider patient referral to haematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.

Pancreatic events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 12.

Table 12: Management guidelines for pancreatic events, including pancreatitis

Event	**Management**
Amylase and/or lipase elevation	
Grade 2	Amylase and/or lipase >1.5-2.0× ULN: • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Asymptomatic with amylase and/or lipase >2.0-5.0× ULN: • Treat as grade 3 event
Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • For recurrent events, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]

Event	Management
Immune-mediated pancreatitis	
Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • For recurrent events, permanently discontinue atezolizumab and ETOP Medical Affairs.[c]
Grade 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Refer patient to GI specialist. • Initiate treatment with 1-2 mg/kg/day i.v. methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 13.

Table 13: Management guidelines for dermatologic events

Event	Management
Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).

Event	Management
Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist, for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to dermatologist, for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 4	• permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Stevens-Johnson syndrome or toxic epidermal necrolysis	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

SCARs

Severe Cutaneous Adverse Reactions (SCARs) are a heterogeneous group of immunologically mediated drug reaction, mainly constituted by erythema multiforme, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). Although rare, these events are potentially fatal. A comprehensive analysis of the data available across the Roche atezolizumab program has identified cases of SCARs following atezolizumab use.

- For suspected SCARs the patients should be referred to a dermatologist for further diagnosis and management

- Atezolizumab should be withheld for patients with suspected SJS or TEN
- Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Neurologic disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative aetiologies. Management guidelines for neurologic disorders are provided in Table 14.

Table 14: Management guidelines for neurologic disorders

Event	Management
Immune-mediated neuropathy	
Grade 1	• Continue atezolizumab. • Investigate aetiology.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Investigate aetiology. • Initiate treatment as per institutional guidelines. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1-2 mg/kg/day oral or i.v. prednisone or equivalent.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Immune-mediated meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients with suspected meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or oedema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate aetiology, should be treated according to the guidelines provided in Table 15.

Table 15: Management guidelines for immune-mediated meningoencephalitis

Event	Management
All grades	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs[a] • Refer patient to neurologist. • Initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

a. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org)

Renal events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common aetiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 16.

Table 16: Management guidelines for renal events

Event	Management
Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the ETOP Medical Affairs.[c]
Grade 3 or 4	• Permanently discontinue atezolizumab and contact the ETOP Medical Affairs. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs.

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after consultation with the ETOP Medical Affairs (medical.affairs@ibcsg.org).

Immune-mediated myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine-kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle-biopsy. One aetiology of myositis is immune-mediated, which is the current concern with atezolizumab.

Table 17: Management guidelines for immune-mediated myositis

Event	Management
Grade 1	• Continue atezolizumab • Refer patient to rheumatologist or neurologist • Initiate treatment as per institutional guidelines.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact ETOP Medical Affairs. • Refer patient to rheumatologist or neurologist.

Event	Management
	• Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroid equivalent to 1-2 mg/kg/day i.v. methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiation corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c]
Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact ETOP Medical Affairs. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day i.v. methylprednisolone or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisolone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1 or better, resume atezolizumab.[b] • If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • For recurrent events, treat as grade 4 event.
Grade 4	• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.[c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day i.v. methylprednisolone or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisolone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to grade 1or better, taper corticosteroids over ≥1 month.

a. Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the ETOP Medical Affairs team (Medical.Affairs@ibcsg.org).

b. If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the ETOP Medical Affairs team (Medical.Affairs@ibcsg.org).

14.1.3. Contraindications with atezolizumab

Atezolizumab is contraindicated for patients with history of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins and to known hypersensitivity to Chinese hamster ovary cell products or any component of the atezolizumab (see the latest version of the ***Atezolizumab IB*** for details).

14.2. Risks associated with bevacizumab

Warnings and precautious for bevacizumab include perforation or fistula; surgery and wound healing complications; haemorrhage; arterial thromboembolic events; venous thromboembolic events; hypertension; posterior reversible encephalopathy syndrome (PRES); proteinuria; infusion reactions; ovarian failure. The most common adverse reactions observed in bevacizumab patients at a rate >10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal haemorrhage, lacrimation disorder, back pain and exfoliative dermatitis (see the latest version of the ***Bevacizumab IB*** for details).

Based on the identified and potential risks associated with bevacizumab, this trial protocol incorporates mandatory safety monitoring procedures and guidance to assist with early diagnosis and rapid management of potential drug-related symptoms.

14.2.1. Known adverse reactions

The following NCI CTC grade 3-5 adverse reactions have been reported:

Very common (≥10%): Febrile neutropenia, leucopenia, thrombocytopenia, neutropenia, anorexia, peripheral sensory neuropathy, dysarthria, headache, dysgeusia, eye disorder, increased lacrimation, hypertension, thromboembolism, dyspnoea, rhinitis, rectal haemorrhage, stomatitis, constipation, diarrhoea, nausea, vomiting, abdominal pain, wound healing complications, exfoliative dermatitis, dry skin, skin discoloration, arthralgia, proteinuria, ovarian failure, asthenia, fatigue, pyrexia, pain, mucosal inflammation, weight decreased.

Common (1 – <10%): Sepsis, abscess, cellulitis, infection, urinary tract infection, anaemia, lymphopenia, hypersensitivity, infusion reaction, dehydration, cerebrovascular accident, syncope, somnolence, headache, congestive heart failure, supraventricular tachycardia, arterial thromboembolism, deep vein thrombosis, haemorrhage, pulmonary haemorrhage, haemoptysis, pulmonary embolism, dysphonia, hypoxia, epistaxis, gastrointestinal perforation, intestinal perforation, ileus, intestinal obstruction, recto-vaginal fistulae,

gastrointestinal disorder, proctalgia, palmar-plantar erythrodysaesthesia syndrome, fistula, muscular weakness, myalgia, back pain, pelvic pain, lethargy.

14.2.2. Special warnings and precautions for use of bevacizumab

Gastrointestinal (GI) perforations and fistulae

Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal fistulae

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-GI fistulae

Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae.

In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of bevacizumab should be considered.

Wound healing complications

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

Necrotising fasciitis

Necrotising fasciitis including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypertension

An increased incidence of hypertension was observed in bevacizumab-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all grades proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome.

Arterial thromboembolism

In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with bevacizumab.

Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.

Venous thromboembolism

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

Bevacizumab should be discontinued in patients with life-threatening (grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions grade ≤3 need to be closely monitored.

Haemorrhage

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be discontinued permanently in patients who experience grade 3 or 4 bleeding during bevacizumab therapy.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in cases of intracranial bleeding.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly.

Pulmonary haemorrhage/haemoptysis

Patients with NSCLC treated with bevacizumab may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (>2.5 ml of red blood) should not be treated with bevacizumab.

Congestive heart failure (CHF)

Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with bevacizumab.

Neutropenia and infections

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, metastatic breast cancer, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions/infusion reactions

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Ovarian failure/fertility

Bevacizumab may impair female fertility. Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with bevacizumab.

14.2.3. Elderly patients

In randomised clinical trials, age >65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischemic attacks and myocardial infarction as compared to those aged ≤65 years when treated with bevacizumab. Other reactions with a higher frequency seen in patients over 65 were grade 3-4 leucopenia, thrombocytopenia; and all grade neutropenia, diarrhoea, nausea, headache and fatigue.

No increase in the incidences of other reactions, including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, congestive heart failure and haemorrhage, was observed in elderly patients (>65 years) receiving bevacizumab as compared to those aged ≤65 years treated with bevacizumab.

14.2.4. Dose modification and treatment interruption for bevacizumab

There are no recommended dose reductions. Bevacizumab should be discontinued in the event of GI perforation, fistula, reversible posterior leukoencephalopathy syndrome (RPLS) and wound healing complications.

The bevacizumab-related AEs hypertension, proteinuria, thromboembolism and haemorrhage inducing any CNS bleeding, as well as any grade 3 or 4 bevacizumab related AEs, should be managed as described in Section 14.2.5 below.

14.2.5. Management guidelines of bevacizumab related toxicities

Treatment with bevacizumab should be temporarily interrupted if one of the following adverse events occurs despite optimal supportive care, when not attributable to the disease under investigation, where the investigator considers the AE of concern to be specifically associated with bevacizumab:

- Any intolerable adverse event regardless of grade
- Any adverse events CTCAE v5.0 grade ≥3 (despite optimal supportive care)

If toxicity resolves or reverts to CTCAE v5.0 grade ≤1 within 21 days of onset and the patient is showing clinical benefit, treatment with bevacizumab may be restarted using the rules below for dose modifications and with discussion and agreement with ETOP Medical Affairs (Medical.Affairs@ibcsg.org) as needed.

If toxicity does not resolve to CTCAE v5.0 grade ≤1 after 21 days, then the patient should be withdrawn from the trial and observed until resolution of the toxicity.

Temporarily suspend bevacizumab for:

- At least 4 weeks prior to elective surgery, see Section 14.2.6
- First venous thromboembolic event grade 3 or 4 requiring full anticoagulation; bevacizumab may be resumed after initiation of therapeutic-dose anticoagulant therapy if the patient is on a stable dose of anticoagulant.

- Severe hypertension not controlled with medical management. Blood pressure should be less than 150 mmHg systolic and 100 mmHg diastolic before bevacizumab is given. If blood pressure is higher, measurement should be repeated and if hypertension is confirmed, antihypertensive medication should be started and bevacizumab should be delayed until blood pressure drops below 150/100 mmHg (See Table 18).
- Proteinuria grade 3; resume bevacizumab once grade 2 (refer to Table 19 for details regarding dipstick and 24-hour urine collection) or less has been attained.
- Grade 3 or 4 bevacizumab-related events (except grad 3 hypertension) occurring for the first time: bevacizumab should be discontinued until toxicity improves to grade 1. When a grade 3 or 4 event occurs for second time, bevacizumab should be discontinued permanently

Discontinue bevacizumab for:

- Arterial thromboembolism (any grade)
- Febrile grade 4 neutropenia and/or grade 4 thrombocytopenia regardless of the relationship to treatment
- Grade ≥3 venous thrombosis/embolism (including pulmonary embolism) and recurrent venous thromboembolic event requiring full anticoagulation
- Gastrointestinal perforations (gastric ulcer, fistula formation in the gastrointestinal tract, intra-abdominal abscess)
- Grade ≥2 fistula formation involving an internal organ
- Cerebral or cardiac ischemic events
- Grade ≥3 left ventricular dysfunction (CHF)
- Wound dehiscence and wound healing complications requiring medical intervention
- Nephrotic syndrome.
- CNS bleeding (any grade) or grade ≥3 bleeding of any kind
- Grade ≥2 haemoptysis
- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathy
- Posterior reversible encephalopathy syndrome (PRES)
- Severe infusion reactions
- Recurring grade 3 or 4 bevacizumab-related event
- A treatment delay of more than 6 weeks

Hypertension

Table 18: Management of bevacizumab-related hypertension

	CTCAE description	**Actions**
Grade 1	Prehypertension (systolic BP 120 to 139 mmHg or diastolic BP 80 to 89 mmHg)	No bevacizumab dose modification
Grade 2	Stage 1 hypertension (systolic BP 140 to 159 mmHg or diastolic BP 90 to 99 mmHg); recurrent or persistent (≥24 hours); symptomatic diastolic BP increase by >20 mmHg; monotherapy indicated	Start anti-hypertensive therapy. Once blood pressure is <150/100 mmHg, patients may continue bevacizumab therapy
Grade 3	Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); more than one drug or more intensive therapy than previously used indicated	Hold bevacizumab for persistent or symptomatic hypertension and discontinue permanently if hypertension is not controlled
Grade 4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Permanently discontinue bevacizumab

Proteinuria

Table 19: Management of proteinuria

	CTCAE description	**Action**
Grade 1	Urine protein level ≤1 g/24 hrs (urine dipstick 1+)	No bevacizumab dose modification
Grade 2	Urine dipstick 2+ to 3+ or urine protein level of >1 g/24 hrs	Patients with 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Suspend bevacizumab until proteinuria is <2 g/24 hrs
Grade 3	Urine dipstick 4+ or urine protein level >3.5g/24 hrs	Withhold bevacizumab. Resume when proteinuria is <2 g/24 hrs.
Grade 4	Nephrotic syndrome	Permanently discontinue bevacizumab

Thrombosis/Embolism

- Arterial thromboembolism (ATE, including pulmonary embolism):

  Permanently discontinue bevacizumab for any grade ATE;

- Venous thromboembolism (grade ≥3)
  - First occurrence: discontinue bevacizumab, until toxicity has improved to grade≤1 within 21 days;
  - Second occurrence: permanently discontinue bevacizumab.

Haemorrhage

- Any grade of CNS bleeding: permanently discontinue bevacizumab. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding of any grade.
- Grade ≥2 haemoptysis: permanently discontinue bevacizumab.
- Grade 3 or 4 bleeding of any other kind: permanently discontinue bevacizumab.

14.2.6. Surgery and wound healing complications

Bevacizumab may adversely affect the wound healing process. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld 4 weeks prior to elective surgery.

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

14.2.7. Contraindications

Bevacizumab is contraindicated in patients with known hypersensitivity to any components of the product and to Chinese hamster ovary cell products or other recombinant human or humanized antibodies (see the latest version of the ***Bevacizumab IB*** for details).

14.3. Risks associated with the combination of atezolizumab and bevacizumab

The safety of the combination of atezolizumab with bevacizumab was assessed in the phase Ib Study GP28328. As of the Clinical Cut-off Date of 30 August 2016, there were 229 safety-evaluable patients enrolled across six treatment arms.

Of the 229 safety-evaluable patients across all treatment arms, 98.7% reported an adverse event, with the most common (≥20%) being fatigue (61.1%), nausea (47.6%), diarrhoea (43.7%), decreased appetite (32.3%), neutropenia (31.4%), anaemia (25.3%), peripheral neuropathy (24.5%), constipation and vomiting (29.3% each), arthralgia and cough (26.6% each), pyrexia (27.1%), and headache (21.8%). These AEs were consistent with the known toxicity profiles of atezolizumab and bevacizumab.

IMmotion 150 is an ongoing randomised Phase II trial of atezolizumab administered as a monotherapy (1200 mg i.v. Q3W) or in combination with bevacizumab (15 mg/kg i.v. Q3W) versus sunitinib (50 mg/day PO 4 weeks on/2 weeks off) in patients with previously untreated advanced RCC. The most frequently reported AEs in the atezolizumab plus bevacizumab combination arm (N= 101) are as follows: fatigue (59.4%), arthralgia (37.6%), hypertension (36.6%), nausea and proteinuria (35.6% each), diarrhoea (33.7%), headache (32.7%), constipation and epistaxis (27.7% each), decreased appetite, rash, and pruritus (21.8% each),

pyrexia (20.8%), hypothyroidism, vomiting, musculoskeletal pain, cough, and dyspnoea (18.8% each), mucosal inflammation (17.8%), and abdominal pain and dysphonia (16.8% each).

IMpower150 is a phase III trial assessing the combination therapy combination of chemotherapy, antiangiogenic treatment and immunotherapy as first-line treatment for advanced non-squamous NSCLC. A total of 1202 patients were randomised to receive either chemotherapy plus atezolizumab; chemotherapy plus atezolizumab plus bevacizumab, or chemotherapy plus bevacizumab. The safety profile of the atezolizumab and bevacizumab plus chemotherapy combination was consistent with the safety profiles of the individual treatments and no new safety signals were identified with the combination. Serious adverse events related to treatment were observed in 25.4% of patients who received atezolizumab and bevacizumab plus chemotherapy compared to 19.3% of those who received bevacizumab plus chemotherapy.[16]

Refer to the ***Atezolizumab Investigator's Brochure*** for detailed study results.

14.4. Contraception, nursing, pregnancy

14.4.1. Contraception

Female patients who are not of childbearing potential due to being postmenopausal (≥2 years without menstruation) or surgically sterilised (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception during the course of the trial.

Women of childbearing potential and sexually active men must use highly effective contraception (methods that result in a failure rate of <1% per year) from the start of protocol treatment until at least 6 months after the last dose (see Section 9.7 for highly effective contraception methods).

14.4.2. Use in pregnancy

Women who become pregnant while participating in the trial must discontinue protocol treatment immediately. The pregnancy must be reported immediately following procedures detailed in Section 15.6.18. Also any pregnancy that occurs in a female partner of a male trial participant must be reported.

The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to ETOP without delay and within 24 hours if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or new-born). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the foetus or new-born to ETOP.

14.4.3. Use in nursing women

It is unknown whether atezolizumab or bevacizumab and its metabolites are excreted in human milk. A risk to the new-born/infant cannot be excluded. Patients who are breast-feeding are not eligible for the trial.

15. Safety parameters and definitions

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

Certain types of events require immediate reporting to the ETOP, as outlined in Section 15.6.18.

15.1. Adverse events

An adverse event (AE) is defined as any untoward medical occurrence that occurs from the date of signature of informed consent until 90 days after the last dose of protocol treatment, regardless of whether it is considered related to a medication.

An AE can therefore be any of the following:

- Any unfavourable and unintended sign (including clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a protocol treatment, whether considered related to the protocol treatment or not.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in protocol treatment or concomitant treatment or discontinuation from protocol treatment.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of protocol treatment (e.g., screening invasive procedures such as biopsies)

Any grade of any observed AE should be reported on the AE eCRFs. Please refer to Section 15.6 for details.

15.2. Adverse reaction (AR)

An adverse reaction (AR) is defined as “any noxious and unintended response to the protocol treatment related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor (ETOP) as having a reasonable causal relationship (see Section 15.6) to the protocol treatment qualify as adverse

reactions. The expression suspected/related means to convey in general that there is evidence or argument to suggest a causal relationship to the protocol treatment.

15.3. Unexpected adverse reaction (UAR)

An unexpected adverse reaction (UAR) is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information.

When the outcome of the adverse reaction is not consistent with the IBs or the summaries of product characteristics (SmPC) this adverse reaction should be considered as unexpected.

15.4. Serious adverse events (SAE)

A serious adverse event (SAE) is defined as any undesirable medical occurrence/adverse drug experience that at any dose:

- results in death (any cause, except progression of cancer under study)
- is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- requires or prolongs inpatient hospitalisation (see Section 15.6.16 for details)
- results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- is a significant medical event in the investigator's judgment (see Section 15.4.1 for details)
- is a congenital anomaly or birth defect (including neonatal deaths and abortions)
- is a secondary malignancy/second primary malignancy (see Section 15.4.2 for details)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to CTCAE; see Section15.6); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

SAEs are required to be reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (*SAE Initial Report and SAE Follow-up Report*). See Section 15.6.18 for detailed reporting instructions.

15.4.1. Significant medical events

Significant medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalisation, or disability, but may jeopardise the patient or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

15.4.2. Secondary malignancies / second primary malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

A second primary malignancy is one that is unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

15.4.3. Exceptions to the SAE definition

The following situations do not need to be reported as SAEs:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by protocol treatment.
- A hospitalisation which was planned before the patient consented for trial participation and where admission did not take longer than anticipated (see also Section 15.6.16).
- A hospitalisation planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (serious) AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen significantly.
- Progression or death due to worsening of cancer under study

15.5. Adverse events of special interest (AESI)

The following events of special interest (AESI) are not necessarily SAEs, but are required to be reported by the investigator to ETOP as such on the SAE eCRFs (***SAE Initial Report and SAE Follow-up Report***) by indicating that this is an "adverse event of special interest".

AESIs are required to be reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***). See Section 15.6 for detailed reporting instructions.

The AESIs for this trial are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST >3 × ULN (or >3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 × ULN (of which ≥35% is direct bilirubin)
    - Treatment-emergent ALT or AST >3 × ULN (or >3 × baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune haemolytic anaemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

15.6. Methods and timing for capturing and assessing safety parameters

The investigator is responsible for ensuring that all adverse events (see above for definitions) are recorded on the ***Adverse Events eCRF*** and reported to ETOP in accordance with the instructions provided in this section.

For each adverse event recorded on the ***Adverse Events eCRF***, the investigator will make an assessment of seriousness, severity, and causality (see below for details).

15.6.1. Adverse event reporting period

All AEs, regardless of relationship to the protocol treatment, will be reported from the date of signature of informed consent until 90 days after the last dose of protocol treatment. After this period, the investigator is not required to actively monitor patients for AEs; however, ETOP should be notified if the investigator becomes aware of any post-study SAEs or AESIs that are at least possibly related to previous protocol treatment.

During protocol treatment and until 90 days after the last dose, investigators should seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by trial personnel, will be recorded in the patient's medical record and on the ***Adverse Events eCRF***.

15.6.2. Eliciting adverse event information

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

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

15.6.3. Assessment of severity of adverse events

The adverse event severity grading scale for the CTCAE v5 will be used for assessing adverse event severity. The CTCAE is available for downloading on the internet at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

For adverse events that are not specifically listed in the CTCA, the following toxicity grading scale will be used:

- **Grade 1** = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- **Grade 2** = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- **Grade 3** = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible

- **Grade 4** = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable
- **Grade 5** = Death – the event results in death

The (serious) AE severity grade provides a qualitative assessment of the extent or intensity of a specific event, as determined by the investigator or as reported by the patient. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to trial drug. A severe event may be of relatively minor medical significance (such as severe headache). The term "severe" is **not** the same as "serious", which is based on patient/event **outcome** or **action criteria** associated with events that pose a threat to a patient's life or functioning.

15.6.4. Assessment of causality of adverse events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to protocol treatment. The following guidance should be taken into consideration:

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

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

The investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE following the definitions indicated below:

Not suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected	The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Table 20: Relationship to the protocol treatment

Not suspected	Suspected / related to protocol treatment
- unrelated - unlikely	- possible - probable - definite

15.6.5. Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the ***Adverse Events eCRF*** and avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field on the ***Adverse Events eCRF***.

15.6.6. Diagnosis versus signs and symptoms

A diagnosis (if known) should be recorded on the ***Adverse Events eCRF*** rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the ***Adverse Events eCRF***. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

15.6.7. Adverse events that are secondary to other events

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

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

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

15.6.8. Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the ***Adverse Events eCRF***. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the severity of the event should be updated on the ***Adverse Events eCRF***. If the event becomes serious, it must be reported to ETOP immediately submitting the completed ***SAE Initial Report and SAE Follow-up Report*** eCRF in English within 24 hours of awareness in the EDC system ETOPdata. The ***Adverse Events eCRF*** should be updated by changing the event from "non-serious" to "serious".

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

15.6.9. Abnormal laboratory values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the ***Adverse Events eCRF*** (see 15.6 for details on recording adverse events).

15.6.10. Abnormal vital sign values

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

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

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

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

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

15.6.11. Infusion-mediated reactions

Adverse events that occur during or within 24 hours after treatment administration and are judged to be related to protocol treatment should be captured as a diagnosis (e.g., "infusion-

related reaction"). Infusion-related reactions are required to be reported as AESIs (see Section 15.5) on the **SAE eCRFs** by indicating that this is an "adverse event of special interest". If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded separately. If a patient experiences both a local and systemic reaction to the same dose of protocol treatment, each reaction should be recorded separately with signs and symptoms also recorded separately.

15.6.12. Abnormal liver function tests

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

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

The most appropriate diagnosis or the abnormal laboratory values, if a diagnosis cannot be established, should be reported to ETOP immediately (i.e., no more than 24 hours after learning of the event), on the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***).

15.6.13. Deaths

For the BEAT-meso protocol, mortality is the primary efficacy endpoint. Deaths that occur during the protocol-specified adverse events reporting period (e.g. during protocol treatment and within 90 days after last dose of protocol treatment) that are attributed by the investigator solely to progression of the underlying disease (MPM) should be recorded on the ***Death eCRF***.

All other on-trial deaths, regardless of relationship to the protocol treatment, must be recorded on the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***) and immediately (within 24 hours) reported to ETOP. In addition, death events should be recorded on the ***Death eCRF***.

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

If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***).

If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

15.6.14. Pre-existing medical conditions

A pre-existing medical condition is one that is present at the screening visit for this trial. Such conditions should be recorded on the ***Baseline eCRF*** (baseline symptoms will be recorded on the ***Adverse Events eCRF***).

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

15.6.15. Lack of efficacy or worsening of malignant pleural mesothelioma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the updated modified RECIST criteria for mesothelioma v1.1 (mRECIST v1.1). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

15.6.16. Inpatient hospitalisation or prolonged hospitalisation

An inpatient hospitalisation is defined as a hospital stay equal to, or greater than, 24 hours. Any adverse event that results in hospitalisation (i.e., inpatient admission to a hospital) or prolonged hospitalisation should be documented and reported as a serious adverse event, except as outlined below.

Hospitalisations occurring under the following circumstances are <u>not</u> considered to be SAEs and should not be reported as an adverse event or a serious adverse event:

- elective surgery, for pre-existing conditions and planned prior to trial entry
- occur on an outpatient basis and do not result in admission (hospitalisation <24h)
- are part of the normal treatment or monitoring of the studied treatment

15.6.17. Adverse events associated with an overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of protocol treatment is not itself an AE, but it may result in an AE.

All AEs associated with an overdose or incorrect administration of the protocol treatment are required to be reported on the ***Adverse Events eCRF***.

If the associated adverse event fulfils the seriousness criteria, the event should be reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing by completing the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***).

15.6.18. Reporting of serious adverse events and adverse events of special interest

Any SAE, whether related to protocol treatment or not, or any AESI will be reported from the date of signature of informed consent until 90 days after the last dose of protocol treatment. Information about all such events will be collected and recorded on the SAE eCRFs (***SAE Initial Report and SAE Follow-up Reports***).

After completion of protocol treatments, report all SAEs beyond 90 days that are considered at least possibly related to previous protocol treatment. Cases of secondary malignancies and congenital abnormalities and neonatal deaths are to be considered as SAEs, regardless of whether they occur during or after protocol treatment. These events should be reported during the whole trial duration on the serious Adverse Events eCRFs (***SAE Initial Report and SAE Follow-up Reports***)

To ensure patient safety, ETOP must be informed of each SAE and AESI using the procedures described below:

- Any SAE and AESI must be reported by submitting the completed ***SAE Initial Report and SAE Follow-up Report*** eCRF in English within 24 hours of awareness in the EDC system ETOPdata.
- Queries may be issued by the ETOP safety office; a timely response by the investigator to all SAE-related queries is crucial.
- At the time of initial report, also the ***SAE Follow-up Report eCRF*** must be submitted (even if there is no final outcome). The SAE and AESI outcome must be updated within 15 days after initial reporting. In case the SAE or AESI is reported as ongoing after 15 days, the CRF must be updated at final outcome.

Submission of SAE is done via the EDC system, or in case of unavailability, by sending the SAE form by fax to the ETOP safety office:

+41 31 389 92 29

As soon as the EDC system is available again, the SAE eCRF has to be completed and submitted by the site.

The ETOP safety office will inform safety and other appropriate persons at F. Hoffmann-La Roche Ltd. about all SAEs within 24 hours of receipt at the ETOP safety office.

The ETOP safety office will review the SAE and prepare a summary report of all SAEs received. Listings of SAEs will be prepared as required.

The ETOP safety office will assess serious adverse events for expectedness. Any suspected unexpected serious adverse reactions (SUSARs) occurring in this trial qualify for expedited

reporting and ETOP will notify the appropriate regulatory authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

15.6.19. Reporting requirements for pregnancies

Patients who are not of childbearing potential due to being postmenopausal (2 years without menstruation) or surgical sterilisation (oophorectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial. All other patients are considered to be of childbearing potential and must use adequate contraception throughout the trial.

Women of childbearing potential and sexually active men must use highly effective contraception during protocol treatment and until at least 6 months thereafter. Please refer to Section 9.7 for highly effective contraception methods.

Abortions

Any abortion (miscarriage, spontaneous, induced or elective abortion) should be classified as an SAE (as the ETOP as the sponsor considers abortions to be medically significant) and reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***).

Congenital anomalies/birth defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the protocol treatment or the female partner of a male patient exposed to the protocol treatment should be classified as an SAE and reported to ETOP immediately (i.e., within 24 hours after awareness of the event) by completing the SAE eCRF (***SAE Initial Report and SAE Follow-up Report***).

Maternal exposure

In the case of pregnancy occurring during the course of the trial or within at least 6 months after treatment discontinuation, the investigator shall immediately (within 24 hours after awareness of pregnancy) notify ETOP by completing the ***Pregnancy eCRF*** in ETOPdata in accordance with the SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported (2 weeks) by submitting a second ***Pregnancy eCRF*** in ETOPdata. All neonatal deaths and congenital anomalies/birth defects that occur within 90 days of birth should be reported, irrespective of causality, as SAEs. In addition, any infant death after 90 days, irrespective of causality should also be reported within 24 hours of the investigator's knowledge of the event using the *SAE eCRF*.

Paternal exposure

Pregnancy that occurs in a female partner of a male trial participant is not considered to be an adverse event. The pregnant partner will need to sign an informed Consent Form (ICF) "Pregnant Partner ICF" to allow for follow-up on her pregnancy.

The outcome of all pregnancies (spontaneous abortion or miscarriage, induced or elective abortion, ectopic pregnancy, normal birth or congenital abnormality) must immediately be reported (within 24 hours after awareness of pregnancy outcome) to ETOP by completing the ***Pregnancy eCRF*** in ETOPdata.

15.7. Reference safety information

ETOP as the Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, Institutional Review Boards (IRBs), Ethics Committees (ECs), and applicable health authorities based on applicable legislation.

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

- Atezolizumab IB
- Bevacizumab IB
- Carboplatin Summary of Product Characteristics
- Pemetrexed Summary of Product Characteristics

ETOP as the Sponsor will compare the severity of each event for the trial with the severity in the applicable reference document.

STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

16. Sample size and trial duration

16.1. Sample size determination

The efficacy of atezolizumab, when given to bevacizumab plus standard chemotherapy, will be evaluated based on the primary endpoint of OS, which will be compared between the two randomised treatment groups. In addition, an interim efficacy analysis will be performed at approximately 75% information time, based on O'Brien-Fleming boundaries.

Comparison of OS between the two arms

The target median OS for patients treated with atezolizumab plus bevacizumab and chemotherapy is 24 months, i.e., an absolute increase of 7 months compared to an OS of 17 months for patients treated with bevacizumab and chemotherapy alone (corresponding to an HR of 0.708).

Using the log-rank test at a one-sided significance level of 2.5%, a total of 284 OS events are required in order to detect with 82.1% power, a 7-month increase in median OS (from 17 to 24 months, HR 0.708).

Assuming an accrual rate of 8 patients per month for the first 15 months and 20 patients per month thereafter, and a 5% loss to follow-up by month 24, a total of 400 randomised patients, 200 in each treatment group, need to be followed for an expected duration of 58 months to observe the required number of 284 OS events.

An interim analysis will be performed at the time-point of approximately 75% information fraction (i.e., approximately 213 OS observed events), at 42 months from the first randomisation (power 57%), based on O'Brien-Fleming boundaries calculated by the Lan-DeMets spending function. For the interim, the one-sided p-value boundary will be 0.0096 (HR at boundary =0.726), and for the final 0.0221 (HR at boundary=0.788). Sample size and power calculations are based on the exponential survival assumption and have been performed using the EAST version 6.4 software.

Exploration of possible late-separation effect based on simulations

The effect of a possible late separation of the survival curves (a pattern commonly observed in immunotherapy studies) on the power of interim analysis has been further explored based on simulations. Two alternative scenarios, with separation of survival curves starting either at 3 or 6 months, have been examined. In each scenario, piecewise exponential distributions were considered, with HR=1 for the first 3 or 6 months (no separation of the curves) and appropriately adjusted HR from that time-point onwards, such that the average HR over the whole study duration, (until the required 284 OS events were recorded) would coincide with the trial target HR of 0.708. According to 10,000 simulations performed per scenario, the calculated power at the interim analysis would be 50% and 43% for the 3-month and 6-month separation delay, respectively (with the overall power of the study remaining at 82%).

Simulations have been run in R.

Stratification factors

- Pure epithelioid versus not
- Stage IV (according to 8th TNM classification) versus others

16.2. Trial duration

Clinical visits (until the required 284 OS events for the primary endpoint are recorded) are expected to span approximately 58 months after randomisation of the first patient, assuming an accrual period of 29 months (while 42 months after first randomization we expect to observe the 213 OS events required for the interim efficacy analysis). In addition, a start-up period of 6 months is estimated, as the trial is activated by participating centres. The primary analysis (based on the total 284 OS events needed by the protocol design) will be available approximately 6 years after the inclusion of the first patient.

17. Statistical analysis

17.1. Analysis populations

17.1.1. Efficacy cohort

The efficacy cohort is the ITT cohort of the trial. It will include all eligible patients randomised in the trial. Patients are evaluated in the treatment arms to which they were randomly assigned, regardless of the treatment actually received, including randomised patients who did not receive protocol treatment.

17.1.2. Safety Cohort

The safety cohort will include all patients who have received at least one dose of protocol treatment. Patients will be evaluated according to the treatment they actually received, irrespective of their allocated treatment at randomisation.

17.2. Efficacy analysis

17.2.1. Primary efficacy analysis

The primary efficacy analysis consists of the analysis of the primary time-to-event endpoint OS. It will be based on the efficacy (ITT) cohort, stratified by the randomisation stratification factors.

Median time for OS and corresponding 95% CIs will be estimated by treatment arm, using the Kaplan-Meier method. OS will be compared between the treatment arms based on the stratified log-rank test. The corresponding HR and 95% CI will be derived from Cox proportional hazards models (stratified according to the stratification factors, stage and histology).

The design hypothesis for OS will be evaluated at an overall one-sided level of significance α=2.5%, appropriately allocated to the designed interim and final analysis as described in more detail in the section for the interim below.

Furthermore, multivariate Cox proportional hazards models (stratified according to the randomisation stratification factors) will be constructed, in order to assess the association of OS with treatment, adjusted for a series of prognostic factors, including baseline patient characteristics and tumour characteristics, as well as for available biomarkers. Significant outcome prognostic factors will be elicited using the backwards elimination method (removal $p \geq 0.10$).

More details will be provided in the corresponding Statistical Analysis Plan.

17.2.2. Analysis of secondary efficacy endpoints

Clinical efficacy (including PFS, ORR, DCR, TTF and DoR) will be further assessed and compared between the two treatment arms, overall and stratified by the randomisation stratification factors. Analogous to the primary efficacy analysis, the secondary efficacy analysis will be based on the efficacy (ITT) cohort.

PFS, a time-to-event endpoint, will be analysed in an analogous way as the primary endpoint OS.

ORR and DCR along with corresponding 95% exact-binomial CIs will be presented overall and compared by treatment arm based on the Fisher's exact test and Cochran-Mantel-Haenszel test stratified by the stratification factors of the trial (odds ratio will also be provided). Logistic regression models of the "response" or "disease control" will be further applied to investigate the treatment effect, adjusting for stratification factors and variables of clinical interest.

TTF and DoR will also be compared between the two treatment groups, using log-rank test graphically represented by Kaplan-Meier plots.

17.3. Interim efficacy analysis

An interim efficacy analysis for the primary endpoint OS is planned to be performed when approximately 213 OS events (75% information fraction) have been observed. This is expected to take place approximately 42 months after the randomisation of the first patient. At the time-point of 213 OS observed events, the one-sided p-value boundary is 0.0096 with corresponding HR boundary 0.726 (based on O'Brien-Fleming boundaries calculated by the Lan-DeMets spending function). The one-sided p-value boundary for the final analysis is 0.0221, with corresponding HR=0.788.

In case that a slightly different number of OS events (>213 according to the design) is used for the interim analysis, the corresponding one-sided alpha (p-value boundary) will be re-calculated based on the exact number of observed OS events in the ITT cohort (according, as before, to the Lan-DeMets spending function).

If, in the interim efficacy analysis, the efficacy boundary for OS is crossed in favour of the alternative, a significant benefit for OS will be claimed for the addition of atezolizumab to bevacizumab and standard chemotherapy. The trial can be declared successful and we can proceed to reporting this result as the primary analysis. If the interim boundary is not crossed at the interim analysis, then the study continues to the primary efficacy analysis (when 284 OS events are observed).

17.4. Safety analysis

The safety analysis of the protocol treatments will be based on the safety cohort. The worst AE grade (highest toxicity) observed over the whole treatment period will be displayed and adverse event severity will be graded according to CTCAE v5.0.

Summary statistics by treatment arm will be presented in tabular and graphical format.

17.5. Interim safety analysis

Safety data will be reviewed by the ETOP IDMC on a periodic basis, approximately every 6 months from the time of randomisation of the first patient. Recruitment into the trial will continue while safety is being evaluated. Please refer to Section 28.2 for detailed description of the ETOP IDMC.

17.6. Other exploratory analyses

17.6.1. Quality of life

The LCSS total score, the ASBI (including the 5 symptoms), the three items addressing symptomatic distress, normal activity, and global QoL, and each single symptom will be presented as changes (in absolute values and percentages) from baseline to each time-point according to treatment assignment (ITT analysis). The primary QoL endpoint will be the change in the LCSS total score (average of all 8 items) from baseline to 12 weeks after treatment start.

Differences of at least 10 points (on a 0 to 100 point scale) are defined as the minimum clinically meaningful change in a QoL indicator.[39] This definition was also used in the MAPS trial, which will be a reference trial for interpreting the QoL results.

Mixed-effects linear regression modelling for repeated measures will be used to test the effect of treatment on changes in the LCSS total score, the ASBI, and each single item (i.e., 5 symptom items, 3 global items) with an unstructured covariance structure. The model includes treatment assignment (chemotherapy plus bevacizumab versus chemotherapy plus bevacizumab plus atezolizumab), assessment time-point (categorical: 3, 6, 9, 12, 18, and 24 weeks), and the interactions of the two variables. Models will be adjusted for patient and disease characteristics (including age, sex, smoking status, ECOG performance status, TNM staging) and account for missing responses.

From the model, an estimated mean difference between treatment groups can be calculated with 95% CI for each time-point and compared at 12 and 24 weeks using model contrasts.

Reasons for missing data will be assessed for each scheduled assessment with no available QoL data and presented in frequency tables by treatment arm. In case of 20% or more missing questionnaires, the mechanism of missingness, i.e. missing complete at random (MCAR), missing at random (MAR) or missing not at random (MNAR), shall be investigated and appropriate alternative analysis approaches might be applied.

17.6.2. Summaries of treatment group comparability

Demographic and baseline characteristics (including age, sex, smoking status, ECOG performance status, TNM staging, medical history) will be summarised using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group. Differences between treatment groups will be statistically assessed based on Fisher's exact test (for categorical variables) and Mann-Whitney test (for continuous variables).

17.6.3. Further exploratory analyses

Further exploratory analyses include descriptive statistics by treatment arm for responses according to PD-L1/PD-L2 expression level and tumour mutational burden.

DATA COLLECTION AND MANAGEMENT

18. Quality of life assessment

18.1. Quality of life measure

QoL will be assessed by the LCSS-Meso an 8-item questionnaire including five symptoms (i.e., appetite loss, fatigue, cough, dyspnoea, and pain) and three items addressing symptomatic distress, normal activity, and global QoL.[18,21,23]

Psychometric testing revealed that the LCSS-Meso was enhanced by deletion of the haemoptysis item. The LCSS-Meso demonstrated that it is feasible, has acceptable reliability, good internal consistency for the eight-item measure, and good test-retest reliability. Content, construct and criterion-related validity was supported based on the results obtained in two clinical trials of pemetrexed in patients with pleural mesothelioma.[18]

An average of all eight items is used for a total score. A sub-score using the mean of all five major symptoms or ASBI, the single global QoL item, and/or individual items to report specific areas of change can be used.

All items are measured by VAS using 100-mm lines to assess the intensity of patient responses addressing the time frame of the past day (operationalized: last 24 h). Each item is assigned an individual score corresponding to the length of the line representing intensity as marked by the patient (with 0 as the lowest and 100 mm as the highest rating). Higher scores indicate a worse condition. The LCSS, and therefore also the adapted meso-specific scale is available in many translated versions (http://www.lcss-ql.com).

18.2. Quality of Life data collection and management

All patients who signed the informed consent of this trial need to complete the QoL questionnaire at the defined time-points. There will be no patient selection within participating institutions. Reasons for non-completion of QoL questionnaires will be documented.

As part of the informed consent, the patients need to be informed that there will be repeated QoL assessments over a period of 6 months (24 weeks). The paper-based QoL questionnaire (LCSS-Meso) is to be completed by the patient during the visits at the hospital, i.e.: within 3 days before the administration of treatments in cycles 2-5 (i.e., at weeks 3, 6, 9 and 12) and cycles 7 and 9 (i.e., at weeks 18 and 24) **OR** until end of protocol treatment, whichever is first. It is important that the QoL questionnaire is completed before any diagnostic procedures or communication of diagnostic or prognostic information to the patient, and before trial treatment is given.

For detailed instructions on the QoL assessment, please consult the ***BEAT-meso Procedures Manual***. At the first QoL assessment, the questionnaire has to be explained to the patient, with particular emphasis on making sure the patient understands the visual analogue response format. All questions in the QoL questionnaire must be answered. The completed questionnaire is to be checked while the patient is still present. If necessary, the patient should be asked to fill in missing answers.

If the patient does not fill in a QoL questionnaire, please complete on an empty QoL form the patient ID, the date the QoL assessment should have been done, and the reason why it has not been completed (refer to the corresponding codes on the form).

Completed QoL questionnaires have to be entered on-line at the EDC facility ETOPdata in a timely manner. A copy of the completed QoL questionnaire has to be uploaded to ETOPdata in a timely manner by the site staff member. The original forms have to be filed on site.

19. Case report forms and documentation

Data will be entered on-line in the EDC facility ETOPdata. Only electronic eCRFs will only be available, no paper forms will be used. The only exception concerns the SAE form and pregnancy form in the case of EDC system unavailability.

19.1. Case report forms schedule

Table 21: Case report form schedule

eCRF in ETOPdata	To be completed
EL - Eligibility Check and Randomisation	Within 42 calendar days of written informed consent signature
B - Baseline	Within 14 calendar days after randomisation
TA - Tumour Assessments	Baseline before randomisation: within 14 calendar days after randomisation; After randomisation: within 14 calendar days of date of each radiological imaging.
CM – Concomitant Medications	Continuously from date of randomisation to 90 calendar days after last dose of protocol treatment; - within 14 calendar days from randomisation for medications taken by the patient at the time of randomisation or within 14 days prior to randomisation; - within 14 calendar days of awareness.
PTV – Protocol Treatment Visit	Within 14 calendar days after each treatment visit.
AE - Adverse Events	Continuously from date of Informed Consent signature to 90 calendar days after last dose of protocol treatment; - within 14 calendar days of awareness of AE.
SAE IR - Serious Adverse Event Initial Reports	Continuously from date of Informed Consent signature to 90 calendar days after last dose of protocol treatment; - within 24h of awareness of SAE or AESI; All SAEs and AESIs must be submitted via ETOPdata, submission via fax to ETOP safety office only in case of unavailability of ETOPdata.
SAE FU - Serious Adverse Event Follow-up Reports	At the time of initial report, also the SAE Follow-up Report eCRF must be submitted (even if there is no final outcome). To be updated within 15 calendar days of completion of initial SAE or AESI report. If event was not resolved after 15 calendar days, the CRF must be updated at final outcome.

eCRF in ETOPdata	To be completed
QoL – Quality of Life	Baseline before randomisation: within 14 calendar days after randomisation; After randomisation: within 28 calendar days after completion of questionnaire.
EoT - End of Treatment	Within 14 calendar days after End of Treatment visit.
FU - Follow-up	Within 14 calendar days after each follow-up visit.
D - Death	Within 14 calendar days after death.
P - Pregnancy	Maternal exposure: Within 24h after awareness of pregnancy; Within 14 calendar days of end of pregnancy. Paternal exposure (pregnancy in a female partner of a male trial participant): Within 24 hours after awareness of pregnancy outcome.
WC/LFU – Withdrawal of Consent / Lost to Follow-Up	Within 14 calendar days of awareness of withdrawal of consent or loss to follow-up.
BMT - Biological Material Tracking	This eCRF is to be completed incrementally. Entries are to be made: - within 4 weeks after randomisation: for information pertaining to "FFPE Tumour tissue: at baseline" (prior to randomisation); - immediately after local storage of blood samples (on same day): for information pertaining to "Blood samples at baseline", "Blood samples at cycle 3" and "Blood samples at Progression"; - within 14 calendar days of progression: for information pertaining to "FFPE Tumour tissue at progression" (after protocol treatment, strongly recommended); - immediately (on same day) after submission of material (FFPE) for central biobanking: for field "Date Specimen sent to Central Lab".

19.2. Documents to be uploaded on ETOPdata

- Copy of pathology report
- Copy of quality of life form

19.3. Queries Resolution Schedules

Table 22: Queries resolution schedule

Queries	To be resolved
SAEs-related queries	Within 24 hours of queries establishment
Other queries	Within 7 calendar days of queries establishment
Before interim analysis	Within the time indicated in the email announcing the date of the database lock.

20. Source data documentation

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 22.

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

21. Use of computerized systems

When clinical observations are entered directly into a trial site's computerised medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerised systems used in clinical research. An acceptable computerised data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change. ETOPdata is the EDC system used in this trial.

22. Record retention

Records and documents pertaining to the conduct of this trial and the distribution of the IMP, including eCRFs, electronic or paper (if applicable), patient informed consent statement, printouts from laboratory test results, drug inventory and destruction logs, and all other

information collected during the trial, must be retained by the Principal Investigator for at least 25 years after completion or discontinuation of the trial or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor (ETOP). In the event that the principal investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer has to be given to the Sponsor (ETOP) and the local ethics committee at least one month in advance.

QUALITY CONTROL AND QUALITY ASSURANCE

ETOP conducts trials according to the Good Clinical Practice (GCP) guidelines. The safety and well-being of the trial participants and the data quality is managed using a risk-based approach according to the Integrated Addendum to ICH E6 (R2).

23. Quality Control

23.1. Data quality control / central monitoring

The Trial Data Manager will perform computerised and manual consistency checks on newly entered data on the eCRFs. Queries will be issued in case of inconsistencies (see Section 19.1). Consistent forms will be validated by the Trial Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies. In addition, the ETOP Medical Affairs reviews each case at specific time points.

23.2. Onsite and remote monitoring

At regular intervals during the clinical trial, the participating sites will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review trial progress, investigator and patient compliance with clinical trial protocol requirements and any emergent problems. The frequency of monitoring visits and extent of source data verification will be described in the trial monitoring plan.

Monitoring visits will include but are not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, dispensing protocol treatment, compliance with protocol, drug accountability, concomitant therapy use, quality of data and storage of blood and serum samples.

24. Quality assurance

ETOP conducts audit visits of institutions participating in ETOP trials on a risk-based approach. These audits are performed to provide assurance that the rights, safety and wellbeing of trial participants are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and

to assess the quality of the data. These audits consist of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

By accepting to participate in this protocol, the investigator agrees that ETOP, any third party (e.g. a CRO) acting on behalf of the ETOP, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to qualified personnel from ETOP or its designees. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives, etc.). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

ETHICAL CONSIDERATION

25. Compliance with laws and regulations

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in ICH GCP Guidelines with Integrated Addendum E6(R2) (November 2016) or with local law if it affords greater protection to the patient. For studies conducted in the European Union/European Economic Area (EU/EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

25.1. Ethical Review Board/Institutional Review Board

All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. The Ethical Review Board/Institutional Review Board (ERB/IRB) decision must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent.

The ERB/IRB written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title and version number), and of the patient informed consent. Documentation of Ethics Committee approval must be sent to the ETOP coordinating office prior to enrolment of the first patient.

Any modifications made to the protocol must be submitted to the appropriate ERB/IRB for information or approval in accordance with local procedures and regulatory requirements and to health authorities if required.

Once approved or acknowledged by the appropriate ERB/IRB and by the health authorities (if required), the investigator shall implement the protocol modifications. Protocol

modifications for urgent safety matters may be directly implemented following the instructions of ETOP.

25.2. Regulatory approval procedures

If applicable, in addition to the approval of the ethics committee according to national legislation, the protocol, protocol related documents including patient information and informed consent and other documents as required locally must be submitted to and be approved by the health authority. Documentation of health authority approval must be sent to the ETOP coordinating office prior to participating centre activation.

26. Patient Informed Consent

Informed consent for each patient will be obtained prior to initiating any trial procedures in accordance with the “patient information and informed consent" (see Appendix 1). Once signed and dated, a copy of the informed consent must be given to each patient and the original copy must be retained in the investigator’s trial records. The informed consent form must be available in the case of data audits. Verification of signed informed consent and the date signed are required for enrolment into this trial.

The “Declaration of Helsinki” recommends that consent be obtained from each potential patient in biomedical research trials after the aims, methods, anticipated benefits, and potential hazards of the trial, and discomfort it may entail, are explained to the individual by the physician. The potential patient should also be informed of her/his right to not participate or to withdraw from the trial at any time. The patient should be told that material from her/his tumour and blood and serum samples will be stored and potentially used for additional studies not described in this protocol.

If the patient is in a dependent relationship to the physician or gives consent under duress, the informed consent should be obtained by an independent physician. If the patient is legally incompetent (i.e., a minor, or mentally incompetent), informed consent must be obtained from the parent, legal guardian, or legal representative in accordance with the law of the country in which the trial is to take place. By signing this protocol, the investigator agrees to conduct the trial in accordance with GCP and the "Declaration of Helsinki".

ETOP recognises that each institution has its own local, national, and international guidelines to follow with regard to informed consent. Therefore, we provide a template information sheet and informed consent form (Appendix 1), which can be edited to incorporate information specific to your institution. The template patient information sheet (PIS) and informed consent (IC) has been written according to ICH guidelines, which state the informed consent should adhere to GCP and to the ethical principles that have origin in the “Declaration of Helsinki”. The final version should receive the IRB / local EC approval in advance of its use. Centres should send their locally modified PIS/IC to ETOP for review and approval before submitting to their ethics committee.

27. Confidentiality and data protection

ETOP maintains confidentiality standards by coding all patients enroled in the trial and all data and samples collected. A unique Patient ID/Randomisation number will be assigned by the ETOP EDC facility ETOPdata. Patient names are not included in data sets that are transmitted to the ETOP EDC facility ETOPdata, and no patient names are disclosed to the ETOP.

Only the ETOP Patient ID will be used to identify a patient on the eCRF. Identification of patients must be guaranteed at the participating centre. In order to avoid identification errors, centres should keep a Patient Identification Log containing the patients' name, year of birth, and the Patient ID allocated by ETOP.

Biological material will be assigned the same unique identifier. No identifiable / personal data will be stored in the trial database or the biobank in the central labs.

Biological material will be transferred outside the treating institution for central review and correlative translational research. Results of the assays will be coded only by the patient identifier.

Patient medical information obtained by this trial is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form signed by the patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of biomarker analyses, data derived from these analyses will generally not be provided to trial investigators or patients unless required by law. Only the aggregate results of any conducted research will be available.

Data generated by this trial must be available for inspection upon request by representatives of national and local health authorities, ETOP monitoring and audit personnel, representatives, and collaborators, and the IRB/EC for each trial site, as appropriate.

TRIAL GOVERNANCE AND ADMINISTRATION

28. Governance

28.1. Steering Committee

A Steering Committee will be constituted for this trial. The Steering Committee is responsible for maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials. Membership will include the trial chairs and co-chairs, trial statisticians, ETOP officials, representatives from participating institutions and a representative from F. Hoffmann-La Roche Ltd.

28.2. Independent Data Monitoring Committee

The ETOP IDMC is a standing committee of independent experts. Its role is the systematic review of the accumulating data from all ongoing ETOP sponsored trials including accrual, safety and efficacy. The primary mandate of the IDMC is to safeguard the interest and safety of the patients in the trial and to ensure the scientific integrity of the trial. Details of the particular responsibilities and procedures within the ETOP 13-18 BEAT-meso trial are summarised in the ETOP IDMC Guidelines and the trial-specific IDMC Charter.

The trial will be presented for review to the ETOP IDMC at each of their bi-annual meetings. Based on this review, the IDMC will provide recommendations to the trial Steering Committee as described in the IDMC Charter.

Any outcomes of these data reviews that affect trial conduct will be communicated in a timely manner to the investigators for notification of their respective IRBs/ECs if required.

28.3. Clinical trial insurance

ETOP will contract the appropriate liability insurance for this trial. Patients who suffer injuries due to the trial should report them immediately to their physician. The local group/institution should report all alleged claims immediately to the ETOP coordinating office.

29. Administrative issue

29.1. Final report

A final clinical trial report will be written and distributed to health authorities as required by applicable regulatory requirements.

29.2. Publication

The results of the trial will be published according to the ETOP publication guidelines.

29.3. Protocol adherence

Investigators ascertain that they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact ETOP or personnel monitoring the trial to request approval of a protocol deviation, as no deviations are permitted. The investigator should document and explain any deviations from the approved protocol. The investigator should promptly report any deviations to ETOP (sponsor) and to the EC concerned in accordance with the applicable EC policies and procedures. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is developed and activated by ETOP (sponsor) and approved by the IRB/ERB/Independent EC it cannot be implemented. All protocol deviations will be recorded.

REFERENCES

1. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. *Lancet* 2005; **366**(9483): 397-408.
2. Tsiouris A, Walesby RK. Malignant pleural mesothelioma: current concepts in treatment. *Nat Clin Pract Oncol* 2007; **4**(6): 344-52.
3. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21**(14): 2636-44.
4. Fennell DA, Gaudino G, O'Byrne KJ, Mutti L, van Meerbeeck J. Advances in the systemic therapy of malignant pleural mesothelioma. *Nat Clin Pract Oncol* 2008; **5**(3): 136-47.
5. Nowak AK. Chemotherapy for malignant pleural mesothelioma: a review of current management and a look to the future. *Ann Cardiothorac Surg* 2012; **1**(4): 508-15.
6. Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol* 2006; **24**(9): 1443-8.
7. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. *Br J Cancer* 2013; **109**(3): 552-8.
8. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016; **387**(10030): 1837-46.
9. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016; **387**(10031): 1909-20.
10. Gerber HP, Kowalski J, Sherman D, Eberhard DA, Ferrara N. Complete inhibition of rhabdomyosarcoma xenograft growth and neovascularization requires blockade of both tumor and host vascular endothelial growth factor. *Cancer Res* 2000; **60**(22): 6253-8.
11. Mordenti J, Thomsen K, Licko V, Chen H, Meng YG, Ferrara N. Efficacy and concentration-response of murine anti-VEGF monoclonal antibody in tumor-bearing mice and extrapolation to humans. *Toxicol Pathol* 1999; **27**(1): 14-21.
12. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016; **387**(10026): 1405-14.
13. Scagliotti GV, Gaafar R, Nowak A, et al. P2.01: LUME-MeSO: Phase II/III Study of Nintedanib + Pemetrexed/Cisplatin in Patients With Malignant Pleural Mesothelioma: Track: SCLC, Mesothelioma, Thymoma. *J Thorac Oncol* 2016; **11**(10S): S216.
14. Blumenschein G, Jr., Chandler J, Garon EB, et al. PS01.59: CheckMate 370: A Master Protocol of Phase 1/2 Studies of Nivolumab as Maintenance or First-Line ± Standard-of-Care Therapies in Advanced NSCLC. *Journal of Thoracic Oncology*; **11**(11): S307.
15. Gadgeel SM, Stevenson J, Langer CJ, et al. Pembrolizumab (pembro) plus chemotherapy as front-line therapy for advanced NSCLC: KEYNOTE-021 cohorts A-C. *Journal of Clinical Oncology* 2016; **34**(15_suppl): 9016-.
16. Reck M, Socinski MA, Cappuzzo F, et al. Primary PFS and safety analyses of a randomized phase III study of carboplatin + paclitaxel +/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic nsclc (IMPOWER150). *Annals of Oncology* 2017; **28**(suppl_11).
17. Bottomley A, Gaafar R, Manegold C, et al. Short-term treatment-related symptoms and quality of life: results from an international randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an EORTC Lung-Cancer Group and National Cancer Institute, Canada, Intergroup Study. *J Clin Oncol* 2006; **24**(9): 1435-42.
18. Hollen PJ, Gralla RJ, Liepa AM, Symanowski JT, Rusthoven JJ. Measuring quality of life in patients with pleural mesothelioma using a modified version of the Lung Cancer Symptom Scale (LCSS): psychometric properties of the LCSS-Meso. *Support Care Cancer* 2006; **14**(1): 11-21.
19. Moore S, Darlison L, Tod AM. Living with mesothelioma. A literature review. *Eur J Cancer Care (Engl)* 2010; **19**(4): 458-68.
20. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008; **371**(9625): 1685-94.
21. Gelhorn HL, Skalicky AM, Balantac Z, et al. Content validity and electronic PRO (ePRO) usability of the Lung Cancer Symptom Scale-Mesothelioma (LCSS-Meso) in mesothelioma patients. *Support Care Cancer* 2018.

22. Westeel V, Eberst G, Anota A, et al. Impact on health-related quality of life of the addition of bevacizumab to cisplatin-pemetrexed in malignant pleural mesothelioma in the MAPS phase III trial. *J Clin Oncol* 2018; **36 (suppl; abstr 8505)**.
23. Hollen PJ, Gralla RJ, Rittenberg CN. Quality of life as a clinical trial endpoint: determining the appropriate interval for repeated assessments in patients with advanced lung cancer. *Support Care Cancer* 2004; **12**(11): 767-73.
24. Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. *MAbs* 2016; **8**(3): 593-603.
25. Alley E, Lopez J, Santoro A, et al. OA13.03 Long-Term Overall Survival for Patients with Malignant Pleural Mesothelioma on Pembrolizumab Enrolled in KEYNOTE-028. *Journal of Thoracic Oncology*; **12**(1): S294.
26. Goto Y, Okada M, Kijima T, et al. MA 19.01 A Phase II Study of Nivolumab: A Multicenter, Open-Label, Single Arm Study in Malignant Pleural Mesothelioma (MERIT). *Journal of Thoracic Oncology*; **12**(11): S1883.
27. Quispel-Janssen J, Zago G, Schouten R, et al. OA13.01 A Phase II Study of Nivolumab in Malignant Pleural Mesothelioma (NivoMes): with Translational Research (TR) Biopies. *Journal of Thoracic Oncology*; **12**(1): S292-S3.
28. Nowak AK, Stockler MR, Byrne MJ. Assessing quality of life during chemotherapy for pleural mesothelioma: feasibility, validity, and results of using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire and Lung Cancer Module. *J Clin Oncol* 2004; **22**(15): 3172-80.
29. Armato SG, 3rd, Nowak AK. Revised Modified Response Evaluation Criteria in Solid Tumors for Assessment of Response in Malignant Pleural Mesothelioma (Version 1.1). *J Thorac Oncol* 2018; **13**(7): 1012-21.
30. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.
31. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019; **25**(4): 625-38.
32. Adashek ML, Feldman M. Cytokine Release Syndrome Resulting From Anti-Programmed Death-1 Antibody: Raising Awareness Among Community Oncologists. *J Oncol Pract* 2019; **15**(9): 502-4.
33. Feldmann A, Arndt C, Koristka S, Berndt N, Bergmann R, Bachmann MP. Conventional CARs versus modular CARs. *Cancer Immunol Immunother* 2019; **68**(10): 1713-9.
34. Rotz SJ, Leino D, Szabo S, Mangino JL, Turpin BK, Pressey JG. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. *Pediatr Blood Cancer* 2017; **64**(12).
35. Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. *Ther Clin Risk Manag* 2019; **15**: 323-35.
36. McClain K, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet] 2014, [updated 29 October 2018; cited: 17 May 2019]. 2019. https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.
37. Ravelli A, Minoia F, Davi S, et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis* 2016; **75**(3): 481-9.