



## **ETOP 15-19 ABC-lung**

**A randomised non-comparative open label phase II trial of atezolizumab plus bevacizumab, with carboplatin-paclitaxel or pemetrexed, in *EGFR*-mutant non-small cell lung carcinoma with acquired resistance**

**ABC-lung: Atezolizumab, Bevacizumab and Chemotherapy in *EGFR*-mutant non-small cell lung carcinoma**

**Sponsor and Coordinating Group:  
European Thoracic Oncology Platform (ETOP)**

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**In collaboration with F. Hoffmann-La Roche Ltd.**

# Protocol **Amendment 1** Signature Page

## ETOP 15-19 ABC-lung

**A randomised non-comparative open label phase II trial of atezolizumab plus bevacizumab, with carboplatin-paclitaxel or pemetrexed, in *EGFR*-mutant non-small cell lung carcinoma with acquired resistance**

**ABC-lung: Atezolizumab, Bevacizumab and Chemotherapy in *EGFR*-mutant non-small cell lung carcinoma**

**Approved by:**

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Trial Chair

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Date

Rolf Stahel  
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Date

Urania Dafni  
Biostatistician

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Date

Anita Hiltbrunner  
ETOP Director

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Date

# Principal Investigator Protocol **Amendment 1** Signature Page

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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 15 years.

Name of Principal Investigator: \_\_\_\_\_

Institution's name and place: \_\_\_\_\_

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

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# PROTOCOL SUMMARY

## ETOP 15-19 ABC-lung

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### ABC-lung: Atezolizumab, Bevacizumab and Chemotherapy in *EGFR*-mutant non-small cell lung carcinoma

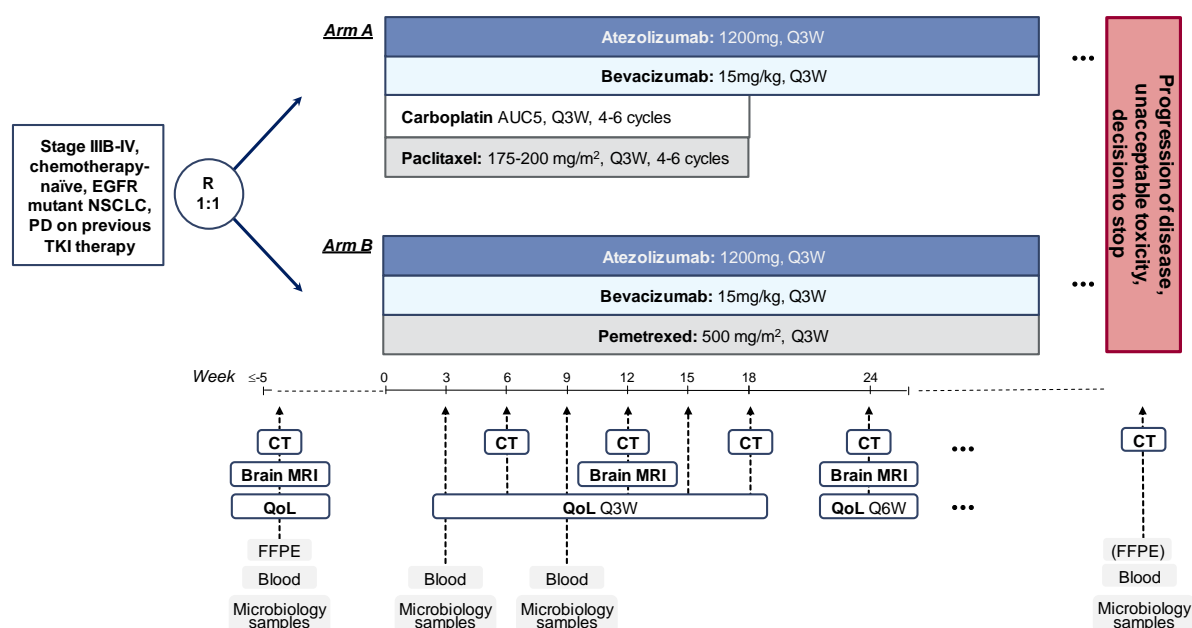
**Sponsor:** European Thoracic Oncology Platform (ETOP)

**Pharma partner:** F. Hoffmann-La Roche Ltd.

**Population:** Patients with chemotherapy-naïve, immune checkpoint inhibitor-naïve, *EGFR*-mutant (L858R or del19) stage IIIB/C (not amenable to radical therapy) or IV non-squamous NSCLC that have relapsed after 1-2 lines of *EGFR* TKI for metastatic disease. Patients with T790M mutation must be previously treated with a third-generation TKI (e.g. osimertinib).

**Design:** Selection design, open-label, randomised trial with two non-comparative parallel arms

**Sample size:** 95 randomised patients



## Treatment:

### Arm A:

- Atezolizumab (1200 mg) Q3W, until PD\*
- Bevacizumab (15 mg/kg), Q3W, until PD
- Carboplatin (AUC5) Q3W, 4-6 cycles
- Paclitaxel<sup>‡</sup> (175-200 mg/m<sup>2</sup>, at the investigators' discretion), Q3W, 4-6 cycles

### Arm B:

- Atezolizumab (1200 mg), Q3W, until PD\*
- Bevacizumab (15 mg/kg), Q3W, until PD
- Pemetrexed (500 mg/m<sup>2</sup>), Q3W, until PD

Treatment will continue until disease progression, toxicity, or patient/physician decision.

\*Atezolizumab treatment beyond RECIST v1.1-defined progression will be allowed if patient is continuing to derive clinical benefit.

‡Asian population: Due to increased haematological toxicities observed in Asian patients in the IMpower150 trial, it is recommended that the starting dose of paclitaxel should be 175 mg/m<sup>2</sup> every three weeks.

## Background:

Lung cancer is the most common cause of death from cancer worldwide. Non-small cell lung carcinoma (NSCLC) represents up to 85% of all lung cancers and at time of diagnosis, approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Activating mutations in the epidermal growth factor receptor (EGFR) are identified in 10-40% of the patients with NSCLC and multiple randomised trials have established EGFR tyrosine kinase inhibitors (TKIs) as standard of care in patients with advanced NSCLC harbouring sensitising *EGFR* mutations (1-2).

However, despite the success of targeted treatment, acquired resistance and disease progression inevitably occur. A number of mechanisms of acquired resistance in patients treated with a first-generation EGFR TKI (erlotinib, gefitinib) or second-generation EGFR TKI (afatinib, dacomitinib) have been described with the most common mechanism of resistance being the emergence of the T790M mutation in *EGFR* in about 50-60% of patients after EGFR TKI failure (3-5).

The standard treatment in patients harbouring EGFR T790M mutations is osimertinib, a third-generation EGFR TKI (1-6). In patients without an EGFR T790M mutation and with acquired resistance to EGFR TKI, or in patients who have progressed after 1<sup>st</sup> line osimertinib, the standard treatment is platinum based doublet chemotherapy (1).

Atezolizumab is a humanised monoclonal antibody against PD-L1. Atezolizumab is indicated for the treatment of patients with metastatic NSCLC who have progressed during or following platinum-based chemotherapy and on targeted therapy, for patient with *EGFR* or *ALK* genetic alterations.

The randomised phase III IMpower150 trial tested atezolizumab in combination with bevacizumab and carboplatin/paclitaxel (ABCP) versus bevacizumab and carboplatin/paclitaxel alone (BCP) in patients with metastatic NSCLC who had not previously received chemotherapy. Progression-free survival (PFS) for patients without an *EGFR* or *ALK* genetic alterations was longer in the ABCP than in the BCP group [8.3 months vs. 6.8 months; HR 0.62; 95% CI 0.52-0.74;  $P < 0.001$ ]. Median OS in patients with wild-type genotype was longer in the ABCP group than in the BCP group (19.2 months vs. 14.7 months; HR 0.78; 95% CI, 0.64-0.96;  $P = 0.02$ ).

The combination of atezolizumab, bevacizumab and chemotherapy was well tolerated (7-9) and its safety profile was consistent with the safety profile of the individual drugs with no new safety signals reported.

In a subgroup analysis of patients with *EGFR* mutations or *ALK* translocations, benefit was seen with ABCP versus BCP for PFS (unstratified HR, 0.59; 95% CI, 0.37-0.94) and for OS (unstratified HR 0.54; 95% CI 0.29-1.03). Interestingly, no OS benefit was seen with atezolizumab plus chemotherapy versus bevacizumab plus chemotherapy in *EGFR/ALK* mutant NSCLC (unstratified HR, 0.82; 95% CI, 0.49-1.37) suggesting that it is the combination of atezolizumab and bevacizumab plus chemotherapy that leads to the clinical benefit in this patient population. Based on these results, the European Medicines Agency (EMA) has approved ABCP in patients with *EGFR/ALK* mutant NSCLC after failure of appropriate targeted therapies.

The potential importance of combining bevacizumab plus atezolizumab was further underlined in IMpower130, where PFS and OS benefits were seen for patients without *EGFR/ALK* alterations treated with atezolizumab, nab-paclitaxel and carboplatin versus nab-paclitaxel and carboplatin (For PFS: HR 0.64; 95% CI 0.54-0.77, for OS HR 0.79; 95% CI 0.64-0.98) (10).

In a subset analysis of patients with *EGFR/ALK* alterations, no improvement in PFS (HR 0.75; 95% CI 0.36-1.54) and OS (HR 0.98; 95% CI 0.41-2.31) was seen with atezolizumab and chemotherapy versus chemotherapy alone.

The results from IMpower130 further underline the potential synergetic effect when combining atezolizumab and bevacizumab and chemotherapy.

Taken together, these results suggest that VEGF plays an important role in *EGFR*-mutant NSCLC by driving both angiogenesis and immune suppression. The combination treatment with bevacizumab and atezolizumab may have a synergistic effect through the inhibition of VEGF and the activation of the immune response.

We aim to explore the combination of atezolizumab and bevacizumab in patients with *EGFR* mutated NSCLC after failure of standard *EGFR*-targeted therapies, by independently verifying PFS in patients treated with a carboplatin-paclitaxel combination (Arm A) and also explore PFS with an investigational backbone of pemetrexed monotherapy (Arm B). Pemetrexed and bevacizumab are considered standard of care in patients with advanced non-squamous NSCLC.

Furthermore, a randomized phase II study in patients with EGFR TKI resistant NSCLC suggested similar outcomes of pemetrexed/cisplatin versus pemetrexed alone with regards to PFS and OS, preserving the ability to use platinum-based therapy as subsequent treatment (11).

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## **Objectives and endpoints:**

### Primary objective

The primary objective of this study is to explore the clinical efficacy of atezolizumab and bevacizumab combined with chemotherapy in *EGFR*-mutated patients after failure of standard *EGFR*-targeted therapies.

### Secondary objectives

To further assess the efficacy and safety of atezolizumab and bevacizumab combined with chemotherapy.

### Exploratory objectives

To explore the relationship between baseline biomarkers and measures of efficacy to protocol treatment.

To assess exploratory biomarkers in archival and/or fresh tumour tissue, blood samples, oropharyngeal swabs and faecal samples and their association with disease status and/or response to study treatment.

### Endpoints

The primary endpoint is the progression-free survival (PFS) rate at 12 months according to RECIST v1.1. This is defined as the rate of patients without a PFS event by 12 months.

The secondary endpoints include objective response rate (ORR) according to RECIST v1.1, extra-cranial PFS, intracranial PFS, overall survival (OS) and safety (adverse events according to CTCAE v5.0).

The exploratory endpoints are as follows:

- Subgroup efficacy analysis according to:
  - Prior use of third-generation TKI (e.g. osimertinib) or not
  - *EGFR* mutation subtype (deletion 19 versus L858R)
  - PD-L1 expression
- Patient reported quality of life

DNA from tumour and blood samples will be isolated and used for sequencing of specific gene panels and, if feasible, tumour mutation burden. Microbiome analysis will be performed on oropharyngeal swabs and faecal samples.

## Patient selection

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

- Chemotherapy naïve, non-squamous NSCLC, stage IIIB/C (not amenable to radical therapy) or IV. Patients who have received previous adjuvant or neoadjuvant chemotherapy are eligible if the date of last dose of treatment was at least 12 months before randomisation
- Known *EGFR* mutations genotypes by tissue or ctDNA; patients with common mutations (L858R or Del19) and other rare mutations (e.g. S768I, G719X) are eligible
- Measurable or evaluable disease by RECIST v1.1
- Disease progression (during or after) or unacceptable side effects from prior treatment with at least one EGFR TKI (TKI washout period = 7 days).

If most recent line of treatment (1<sup>st</sup> or 2<sup>nd</sup> line) was a third-generation EGFR TKI (e.g. osimertinib):

- Patient must be known to be *EGFR* mutation positive, either on fresh tumour biopsy taken >7 days prior to protocol treatment start or by recent ctDNA analysis (informative ctDNA test, local test).
- T790M genotype is allowed.

If most recent line of treatment (1<sup>st</sup> or 2<sup>nd</sup> line) was a first- or second-generation EGFR TKI (e.g. afatinib, dacomitinib, erlotinib, gefitinib):

- Patient must be known to be tissue EGFR T790M wild type (local test) on most recent line of EGFR TKI or if no tissue re-biopsy, no evidence of T790M on ctDNA but identified L858R, del19, S768I or G719X genotypes (informative ctDNA test, local test).
- Treatment with an EGFR TKI therapy for at least 30 days
- Adequate haematological, renal (CrCl at least 45ml/min) and liver function
- Willing to make available surplus tissue obtained at the time of acquired resistance to EGFR TKI

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

- Prior systemic cytotoxic chemotherapy for advanced stage NSCLC
- Prior therapy with bevacizumab or other anti-angiogenic agent
- Prior immune checkpoint inhibitor therapy
- More than two lines of EGFR TKI therapy
- Known small-cell lung carcinoma (SCLC) or high grade neuroendocrine carcinoma (if progression biopsy has been performed locally)
- Squamous cell histologic subtype
- Known EGFR T790M positive genotype by tissue on most recent EGFR TKI progression or ctDNA and have not received an approved EGFR TKI targeting T790M
- Active or untreated CNS metastases as determined by brain MRI

- Patients with CNS metastases must be non-progressive by RECIST v1.1 and symptomatically stable with no ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed.
- Radiotherapy in target lesions within 4 weeks of randomization
- QTc of grade  $\geq 3$  according to CTCAE v5.0
- Active autoimmune disease that has required systemic treatment in past 2 years
- Active or uncontrolled HIV, tuberculosis, hepatitis B or C infection
- Inadequately controlled hypertension (defined as systolic blood pressure  $>150$  mmHg and/or diastolic blood pressure  $>100$  mmHg). Anti-hypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
- History of haemoptysis ( $\geq 2.5$  ml of bright red blood per episode) within 1 month prior to randomization
- Recent surgery: Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first dose of bevacizumab.
- Serious, non-healing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or  $>1.0$  g of protein in a 24-hour urine collection
- Any unresolved toxicities from prior therapy greater than CTCAE v5.0 grade 1 at the time of starting trial treatment with the exception of alopecia

**Statistical considerations:**

This is a selection design, randomised trial with two non-comparative parallel arms.

The following hypothesis will be tested (independently in each arm):

- $H_0$ : 12-month PFS ( $\pi_0$ )  $\leq 0.18$
- $H_1$ : 12-month PFS ( $\pi_1$ )  $> 0.18$ , evaluated at  $\pi_1 = 0.37$ .

With a sample size of 45 patients per arm, the achieved power is 83%, at a one-sided alpha of 0.025 (attained 0.023). Assuming 5% non-evaluable patients, the required total number of patients for both arms increases to 95.

Stratification according to prior use of third-generation TKI (e.g. osimertinib) (Yes/No) will be used.

Sample size and trial duration:

A total of 95 randomised patients are needed. The patients will be recruited from approximately 25 sites in seven countries.

Clinical visits (until primary analysis) are expected to span approximately 24 months after randomisation of the first patient, assuming an accrual rate of 1-2 patients per months during the first 6 months as the trial is being activated by the participating centres, approximately 12-15 patients per month (total accrual time of 12 months) thereafter, plus 12 months of follow-up for all randomized patients. The primary analysis will be available approximately 2.5 years after the inclusion of the first patient.

# LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic 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
BRAF	v-raf murine sarcoma viral oncogene homolog B1
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
<a href="#">DRESS</a>	<a href="#">Drug Rash with Eosinophilia and Systemic Symptoms</a>
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
HLH	Haemophagocytic Lymphohistiocytosis
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
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LFU	Lost to Follow-up
MAS	Macrophage Activation Syndrome
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
QTC	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumours
ROS1	v-ros UR2 sarcoma virus oncogene homolog 1
RR	Response Rate
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SCARS	<a href="#">Severe Cutaneous Adverse Reactions</a>
SCLC	Small-Cell Lung Carcinoma
SD	Stable Disease
SJS	<a href="#">Stevens-Johnson syndrome</a>
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEN	<a href="#">Toxic Epidermal Necrolysis</a>
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

	Screening Within 5 weeks before randomisation (1)	Treatment Period			PD	End of Treatment Visit (3)	Post treatment visit Every 12 (±2) weeks	
		Arm A Atezolizumab, bevacizumab, carboplatin and paclitaxel (2)	Arm B Atezolizumab, bevacizumab and pemetrexed (2)	Arm A & B In addition at cycle 2 and 4			Before PD	After PD
<u>Written informed consent</u> : before any trial specific evaluations and intervention (4)								
<u>Demographics</u> : Year of birth, gender, race								
<u>Medical history</u> : smoking history, comorbidities and allergies								
<u>Vital signs</u> : PS, blood pressure, heart rate, temperature, body weight, height (only at baseline)								
Baseline symptoms (5)								
Adverse events (5)								
Concomitant medications (6)								
<u>Pathology report</u> (7)								
QoL (8)(7)		Within 3 days before treatment administration in cycles 2-7, then every 6 weeks up to 12 months or until PD						
Survival (9)								
<b>Laboratory tests</b>								
Pregnancy test (10)								
<u>Thyroid function</u> : TSH, with reflex free T3/4 (11)		At every 4 <sup>th</sup> treatment cycle, within 3 days before treatment administration.						
<u>HIV and hepatitis B and C status</u>								

	Screening Within 5 weeks before randomisation (1)	Treatment Period			PD	End of Treatment Visit (3)	Post treatment visit Every 12 (±2) weeks	
		Arm A Atezolizumab, bevacizumab, carboplatin and paclitaxel (2)	Arm B Atezolizumab, bevacizumab and pemetrexed (2)	Arm A & B In addition at cycle 2 and 4			Before PD	After PD
<u>Chemistry</u> : serum albumin, glucose, potassium, sodium, calcium, magnesium, amylase and lipase								
<u>Haematology</u> : haemoglobin, platelet count, white blood cell count including differential (lymphocytes and absolute neutrophil count)								
<u>Coagulation profile (INR)</u>		At every 2 <sup>nd</sup> treatment cycle, within 3 days before treatment administration.						
<u>Liver function tests</u> : total bilirubin, ALT, AST, ALP, GGT and LDH								
<u>Renal function tests</u> : urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault								
<u>Urine analysis</u> : specific gravity, pH, protein (12), ketones, glucose and blood (dipstick permitted); elements and microscopic examination if needed		At every 2 <sup>nd</sup> treatment cycle, within 3 days before treatment administration.						
Treatment								
Atezolizumab (1200mg Q3W) (13)		(14) (12)						
Bevacizumab (15mg/kg Q3W) (13)		(14) (12)						
Carboplatin (AUC5, Q3W) (13)		4-6 cycles						
Paclitaxel (175-200 mg/m <sup>2</sup> , at the investigator’s discretion, Q3W) (13)(15)		4-6 cycles						
Pemetrexed (500 mg/m <sup>2</sup> , Q3W) (13)			(14)					
Further lines of treatment (9)								

	Screening Within 5 weeks before randomisation (1)	Treatment Period			PD	End of Treatment Visit (3)	Post treatment visit Every 12 (±2) weeks	
		Arm A Atezolizumab, bevacizumab, carboplatin and paclitaxel (2)	Arm B Atezolizumab, bevacizumab and pemetrexed (2)	Arm A & B In addition at cycle 2 and 4			Before PD	After PD
Disease evaluation								
Radiological tumour assessment by CT thorax & upper abdomen (16)		(16)					(16)	
Brain MRI (16)		(16)						
TNM categories								
Biological material								
Surplus diagnostic FFPE block for PD-L1 testing	(17)							
Blood samples for translational research	(18)(19)			(18)	(18)			
Oropharyngeal swabs and faecal samples for microbiome analysis	(20)			(20)	(20)			

Mandatory evaluation / intervention

- (1) Evaluations to be done within 5 weeks before randomisation. If examinations were done prior to 5 weeks before randomisation, they have to be repeated.
- (2) Assessments have to be done at every treatment cycle, [within 3 days before treatment administration](#).
- (3) Patients are considered to be on protocol treatment for as long as they receive either chemotherapy, bevacizumab and/or atezolizumab
- (4) Written informed consent: within 6 weeks prior to randomisation
- (5) Adverse event reporting: Adverse events have to be reported on the adverse event form, from the date of randomisation until 90 days after the last dose of protocol treatment. Symptoms present at baseline will be recorded on the adverse event form as well.
- (6) 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.
- (7) [A copy of the pathology report \(including the results from EGFR mutation testing\) should be uploaded in ETOPdata \(all information allowing identification of the patient, e.g., patient's name, day and month of birth, must be removed and the ETOP patient identification number added\)](#)
- (8) Quality of Life: At baseline before randomisation at treatment cycles 2-7, [within 3 days before treatment administration](#) (e.g. at weeks 3, 6, 9, 12, 15 and 18) and thereafter every 6 weeks up to 12 months or until disease progression, 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 a copy of the QoL form to ETOPdata after each assessment](#).

- (9) Survival status and further lines of treatment: to be collected during the follow-up visits beyond progression.
- (10) 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 7 days 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 15.8.1).
- (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 as long as the patient is receiving atezolizumab**, thyroid function test is repeated at every 4<sup>th</sup> cycle, **within 3 days before treatment administration**.
- (12) **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.
- (13) **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)**
- (14) Treatment continues until progression according to the RECIST v1.1 or lack of tolerability, or patient declines further treatment. Atezolizumab treatment beyond RECIST v1.1-defined progression will be allowed if patient is continuing to derive clinical benefit.
- (15) **Asian population: Due to increased haematological toxicities observed in Asian patients in the IMpower150 trial, it is recommended that the starting dose of paclitaxel should be 175 mg/m<sup>2</sup> every three weeks.**
- (16) 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 RECIST v1.1. The same imaging technique, acquisition, and processing parameters should be used for each patient throughout the trial.  
CT-schedule: at baseline within 5 weeks before randomisation. CT-scans have to be repeated every 6 weeks ( $\pm 4$  days) from randomisation for 18 months, followed by every 12 weeks ( $\pm 2$  week) until progression of disease. A CT-scan must be repeated if not done within 6 weeks of the end of treatment visit.  
Brain MRI: at baseline within 5 weeks before randomisation. Brain MRI has to be repeated every 12 weeks ( $\pm 2$  week) until progression of disease.  
**For the readout of the primary endpoint (PFS at 12 months), it is important that patients without progression after 12 month will have a CT scan and brain MRI between week 52 and week 54 after randomisation.**
- (17) Mandatory FFPE tumour material: An FFPE tumour tissue block is preferred (obtained at the time of acquired resistance to prior EGFR TKI). Only if the block is not available, 15 slides of 4-5  $\mu$ m thickness are an acceptable alternative to the block. 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. Cytological specimens are accepted in this trial. A tumour re-biopsy at the time of progression is strongly recommended. An FFPE tumour tissue block or slides should be submitted
- (18) Blood samples:  
 At baseline: 2.5 mL whole blood for DNA analysis, 2.5 mL whole blood for RNA analysis and serum sample from 5 mL blood  
 At cycle 2 and 4 (**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
- (19) **Blood samples at baseline 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 first treatment administration in cycle 1.**
- (20) Microbiological samples:  
 - Oropharyngeal swabs taken at baseline, at cycle 2 and 4 (**within 3 days before treatment administration**), and at disease progression.  
 - Faecal samples at baseline, at cycle 2 and 4 (**within 3 days before treatment administration**), and at disease progression.

# BACKGROUND AND RATIONALE

## 1. Background

### 1.1. Disease background

Lung cancer has been the most common carcinoma in the world for several decades. There were estimated 1.8 million new cases of lung cancer in 2012 (12.9% of the total). It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 millions), 19.4% of the total deaths.<sup>1</sup>

Non-small cell lung carcinoma (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis approximately 70% of NSCLC patients already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of early stage NSCLC patients who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer.<sup>2</sup> Patients presenting with unselected advanced NSCLC have a median overall survival (OS) of 10-12 months.<sup>3</sup>

#### 1.1.1. *EGFR* mutations

Advances in the molecular characterization of NSCLC, especially in the adenocarcinoma histologic subtype, has enabled the identification of key genetic aberrations in NSCLC. These genetic aberrations (driver mutations) occur in oncogenes encoding signalling proteins that are crucial for cellular proliferation and survival. The concept of oncogene addiction is based on the notion that tumours become greatly dependent on the expression of single oncogenes for survival.<sup>4</sup> Molecular aberrations identified in lung adenocarcinoma including mutations in the epidermal growth factor receptor (*EGFR*) and *BRAF* genes, gene rearrangement in anaplastic lymphoma kinase (ALK) and *ROS1* can be exploited with tyrosine kinase inhibitors (TKIs).<sup>5-9</sup> Multiple randomised trials have established EGFR TKIs as standard of care in patients with advanced NSCLC harbouring sensitising *EGFR* mutations.<sup>10</sup>

However, despite the success of molecularly targeted treatment, acquired resistance and disease progression inevitably occur. A number of mechanisms of acquired resistance in patients treated with a first-generation EGFR TKI (erlotinib, gefitinib) or second-generation EGFR TKI (afatinib, dacomitinib) have been described with the commonest mechanism resistance being the emergence of the T790M mutation in EGFR, which is detected in about 50-60% of patients after EGFR TKI failure.<sup>11-13</sup> The standard treatment in patients harbouring EGFR T790M mutations is osimertinib, a third-generation EGFR TKI.<sup>10,14</sup> In patients with

acquired resistance to EGFR TKI and that are EGFR T790M negative, or in patients who have progressed after 1<sup>st</sup> line osimertinib, the standard treatment is platinum based doublet chemotherapy.<sup>10</sup>

#### 1.1.2. Vascular endothelial growth factor

The angiogenic factor, vascular endothelial growth factor (VEGF) plays a critical role in angiogenesis, the growth of new vessels from pre-existing vessels. This process is fundamental to the growth of solid tumours, which rely on the formation of new blood vessels, and it plays a significant role in NSCLC; micro-vessel count is an independent predictor of poor prognosis in patients with NSCLC.<sup>15</sup> In mammals the VEGF family comprises five members: VEGF-A, VEGF-B, PlGF, VEGF-C and VEGF-D.

Clinically, the addition of anti-angiogenic agents to chemotherapy in the treatment of advanced NSCLC have led to OS benefit, and two such agents are now approved for this indication. The anti-angiogenic agent bevacizumab (a monoclonal antibody that inhibits VEGF-A), has been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials in non-squamous NSCLC.<sup>16,17</sup> Bevacizumab in combination with platinum-based chemotherapy followed by maintenance bevacizumab is approved for first-line treatment of patients with advanced non-squamous NSCLC.

Increased VEGF levels has been reported to be associated with resistance to EGFR inhibition<sup>18</sup> and pre-clinical studies suggest that erlotinib resistance may be associated with a rise in both tumour cell and host stromal VEGF.<sup>19</sup>

In addition to its oncogenic properties, VEGF also has immunomodulatory effects through several mechanisms including the inhibition of dendritic cell maturation resulting in down-regulating T-cell activation, reduction in T-cell infiltration and an increase in immunosuppressive immune cells such as regulatory T cells and myeloid derived suppressor cells in the tumour microenvironment.<sup>20-23</sup> In addition, the inhibition of VEGF has been reported to reduce VEGF-mediated inhibition of dendritic cell maturation,<sup>20</sup> increase T-cell tumour infiltration,<sup>23-25</sup> and inhibit T-reg and MDSC expansion.<sup>26,27</sup>

## 1.2. Treatment background

### 1.2.1. Atezolizumab

Atezolizumab (Tecentriq™) is a humanised IgG1 monoclonal antibody targeting programmed death ligand 1 (PD-L1). PD-L1 plays a crucial role in regulating the immune system by reducing the proliferation of antigen specific CD8+ T-cells and controlling the accumulation of foreign antigen-specific T-cells. The up-regulation of PD-L1 is one mechanism utilised by tumour cells to evade the immune system by suppressing cytotoxic T-cell activity, T-cell proliferation and cytokine production. Atezolizumab binds to PD-L1 to inhibit its interaction with PD-1 and B7.1 receptors, resulting in the activation of the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth. Atezolizumab has been engineered with a crystallisable fragment domain modification, which eliminates antibody-dependent cellular cytotoxicity and therefore prevent the depletion of activated T cells.

Atezolizumab is indicated for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy and have progressed on an appropriate FDA-approved targeted therapy if their tumour has *EGFR* or *ALK* genetic alterations. More recently, atezolizumab has been also approved in combination with bevacizumab, paclitaxel and carboplatin (chemotherapy), for the initial (first-line) treatment of patients with metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumour aberrations. The recommended dosage of atezolizumab is 1200 mg as an intravenous infusion every three weeks.

### 1.2.2. Bevacizumab

Bevacizumab (Avastin™) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the interaction of VEGF-A to its receptors (Flt-1 and 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.<sup>28,29</sup>

The addition of bevacizumab to carboplatin and paclitaxel resulted in an increase in median OS from 10-12 months.<sup>17</sup> Based on this study, bevacizumab is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC in combination with carboplatin and paclitaxel.<sup>30</sup> The recommended dosage of bevacizumab is 15 mg/kg as an intravenous infusion every three weeks.

### 1.2.3. Chemotherapy

The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC was reported in a meta-analysis that found platinum-based doublet chemotherapy conferred a 1.5-month improvement in median survival over best supportive care (NSCLC Collaborative Group).<sup>31</sup> In the Big Lung Trial (BLT), patients randomised to chemotherapy had a significantly longer survival than those allocated supportive care with a median survival of 8.0 months versus 5.7 months, respectively (Hazard Ratio (HR) 0.77; 95% Confidence Interval (CI) 0.66-0.89).<sup>32</sup> The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in overall response rate (ORR; approximately 15%-22%) and median survival (7-10 months).<sup>33</sup> The use of maintenance chemotherapy with pemetrexed following initial cisplatin/ pemetrexed was associated with an increased OS to 14 months vs 11 months (HR, 0.78; 95% CI, 0.64-0.96).<sup>34</sup>

### 1.3. Quality of life

Patients with advanced NSCLC often experience serious disease symptoms including fatigue, dyspnoea, loss of appetite, cough and pain, which can adversely affect the physical and functional aspects of patients' quality of life (QoL).<sup>35,36</sup> On the other hand, treatment-related toxicities need to be taken into account when addressing QoL in patient undergoing multi-modality treatment.

In IMpower150, comparing atezolizumab or bevacizumab or both in combination with chemotherapy (carboplatin+paclitaxel), only minimal decreases in overall QoL and physical functioning and minimal increases of treatment-related symptoms (e.g. fatigue, constipation, nausea/vomiting) were observed during induction chemotherapy for all three arms, which recovered after completion of chemotherapy.<sup>37,38</sup> In addition, patients in all three arms reported numerical improvement in lung cancer symptoms while on treatment. These results indicate an overall balance between risk and benefit in terms of QoL when using the combination of atezolizumab with bevacizumab and chemotherapy. Nevertheless, minimizing treatment-related toxicity by using less toxic chemotherapy regimens is important with respect to patients QoL. Several clinical trials in patients with advanced NSCLC show that QoL seems at least to be maintained during long-term pemetrexed maintenance therapy for some symptoms while further impairing others when compared to placebo.<sup>39-41</sup> One randomized phase II trial in patients with EGFR TKI resistant tumours suggested similar QoL outcomes of pemetrexed/cisplatin vs. pemetrexed alone.<sup>42</sup> As treatment burden dominates patients' perspectives on therapy which in turn may affect their treatment decisions<sup>43</sup>, it is important to complement clinical outcomes with patient-reported QoL when investigating different treatment strategies.

## 2. Trial hypothesis

The combination of atezolizumab with bevacizumab and chemotherapy has been explored in several studies. In IMpower150, a randomised phase III trial of atezolizumab, bevacizumab and carboplatin/paclitaxel (ABCP) in patients with metastatic NSCLC who had not previously received chemotherapy, the progression-free survival (PFS) for patients with wild-type genotype (*EGFR* or *ALK* genetic alterations were excluded) was longer in the ABCP than in the BCP group [8.3 months vs. 6.8 months; HR 0.62; 95% CI 0.52-0.74;  $P < 0.001$ ]. Median OS in patients with wild-type genotype was longer in the ABCP group than in the BCP group (19.2 months vs. 14.7 months; HR 0.78; 95% CI, 0.64-0.96;  $P = 0.02$ ). The combination of atezolizumab, bevacizumab and chemotherapy was well tolerated,<sup>37,38</sup> and the safety profile of this regimen was consistent with the safety profile of the individual drugs with no new safety signals reported. In a subgroup analysis of patients with *EGFR* mutations or *ALK* translocations in the IMpower150 study, benefit was seen with ABCP versus BCP for PFS (unstratified HR, 0.59; 95% CI, 0.37-0.94) and for OS (unstratified HR 0.54; 95% CI 0.29-1.03). Interestingly, no OS benefit was seen with atezolizumab plus chemotherapy versus bevacizumab plus chemotherapy in *EGFR/ALK*-mutant NSCLC (unstratified OS HR, 0.82; 95% CI, 0.49-1.37) suggesting that it is the combination of atezolizumab and bevacizumab plus chemotherapy that leads to the clinical benefit observed in this molecular subset. The potential importance of combining bevacizumab plus atezolizumab was further underlined in IMpower130. In this study, benefit was seen in patients without *EGFR/ALK* alterations treated with atezolizumab, nab-paclitaxel and carboplatin versus nab-paclitaxel and carboplatin for PFS (HR 0.64; 95% CI 0.54-0.77) and OS (0.79; 95% CI 0.64-0.98).<sup>44</sup> In a subset analysis of patients with *EGFR/ALK*-mutant NSCLC, no improvement in PFS (HR 0.75; 95% CI 0.36-1.54) and OS (HR 0.98; 95% CI 0.41-2.31) was seen with atezolizumab and chemotherapy versus chemotherapy. The results from IMpower130 further underline the potential effect of combining atezolizumab and bevacizumab and chemotherapy as seen with the IMpower150 regimen in patients with *EGFR/ALK*-mutant disease.

Taken together, the pre-clinical and clinical data suggests VEGF may play an important role in *EGFR*-mutant NSCLC by driving both angiogenesis and immune suppression. Bevacizumab is active in preclinical *EGFR* TKI acquired resistance models and is also an immunomodulator, enhancing the benefits of atezolizumab.<sup>19,23</sup> The combination of bevacizumab and atezolizumab maybe synergistic through the inhibition of VEGF immune suppression and reversal of PD-L1-mediated immune inhibition.<sup>45</sup>

## 2.1. Benefit-Risk Assessment

### 2.1.1. Potential benefits

In subset analysis of IMpower150, the combination of ABCP in patients with advanced NSCLC harbouring *EGFR* mutations was associated with an improvement in PFS. The current standard of care following failure of EGFR TKI in *EGFR*-mutant NSCLC is chemotherapy. With the exception of IMpower150 and IMpower130 studies, other studies of immune checkpoint inhibitors either as single agent or in combination have excluded patients with *EGFR*-mutant NSCLC. Hence there is a considerable unmet clinical need to further extend the efficacy of immune checkpoint inhibitors in chemotherapy naïve patients with *EGFR*-mutant NSCLC with acquired resistance to EGFR TKI.

The PFS benefit observed with carboplatin-paclitaxel-bevacizumab-atezolizumab in chemotherapy naïve *EGFR*-mutant NSCLC with acquired TKI resistance is encouraging but requires independent replication as this was an exploratory endpoint. Therefore, we aim to explore the combination of atezolizumab and bevacizumab in patients with *EGFR*-mutant NSCLC with acquired EGFR TKI resistance by independently verifying the PFS in patients treated with carboplatin-paclitaxel combination, and also explore the PFS with an investigational backbone of pemetrexed monotherapy in patients with *EGFR*-mutant NSCLC after failure of standard EGFR-targeted therapies. The investigational chemotherapy backbone of pemetrexed and bevacizumab was selected as pemetrexed-based treatment is a standard of care in patients with advanced non-squamous NSCLC.<sup>10,46</sup> Furthermore, a randomized phase II trial in EGFR TKI resistant patients suggested similar outcomes of pemetrexed/cisplatin vs. pemetrexed alone with regards to PFS and OS, preserving the ability to use platinum-based therapy as subsequent treatment.<sup>42</sup>

### 2.1.2. Potential risks

The safety profile of ABCP was consistent with the safety profiles of the individual agents including the rate of haemorrhagic events caused by bevacizumab. In IMpower150, no new safety signals were identified with ABCP. The frequency of treatment-related serious adverse events was similar to that in previously reported studies of chemotherapy combined with immune checkpoint inhibitors. In particular, the incidence and nature of immune-related adverse events in the ABCP group were similar to those with atezolizumab monotherapy. Adverse events were mostly transient and were limited to the chemotherapy induction phase whereas the frequency of serious adverse events effects during maintenance therapy was low. The absence of carboplatin in the arm of atezolizumab, bevacizumab and pemetrexed is expected to be associated with lower treatment related adverse events. However, there is a risk patients may not respond to treatment and may experience a decline in performance status related to progression of NSCLC and therefore may not be fit to receive subsequent therapies for which they would otherwise have been eligible. Investigators should make every effort to fully inform patients of this risk.

## OBJECTIVES AND ENDPOINTS

### 3. Objectives

#### 3.1. Primary objective

The primary objective of this study is to explore the clinical efficacy of atezolizumab and bevacizumab combined with chemotherapy in patients with *EGFR*-mutant advanced NSCLC after failure of standard EGFR TKIs.

#### 3.2. Secondary objectives

3.2.1. To evaluate secondary measures of clinical efficacy: objective response rate (ORR), extra-cranial PFS, intracranial PFS and OS.

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

### 4. Endpoints

#### 4.1. Primary endpoint

4.1.1. Progression-free survival rate at 12 months according to RECIST v1.1

#### 4.2. Secondary endpoints

4.2.1. Objective response (OR) according to RECIST v1.1

4.2.2. Extra-cranial PFS

4.2.3. Intracranial PFS

4.2.4. Overall survival, including OS rate at 12 months.

4.2.5. Adverse events according to CTCAE v5.0

4.2.6. Patient reported quality of life

### **4.3. Exploratory studies**

The exploratory endpoints are as follows: subgroup analysis according to EGFR subtype, prior use of third-generation TKI or not and according to PD-L1 expression levels.

DNA from tumour and blood samples will be isolated and used for sequencing of specific gene panels and, if feasible, tumour mutation burden. Microbiome analysis will be performed on oropharyngeal swabs and faecal samples.

### **4.4. Endpoint definition**

#### **4.4.1. Progression-free survival rate at 12 months**

The PFS rate at 12 months is the primary endpoint of this trial. It is defined as the rate of patients without a PFS event at 12 months from randomisation. PFS is defined as the time from the date of randomisation until documented progression (according to RECIST v1.1) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if the patient is lost to follow-up or refuses further documentation of follow-up.

#### Extra-cranial progression-free survival

Extra-cranial PFS is the time from randomisation to documentation of disease progression outside the central nervous system (CNS) as per RECIST v1.1 or death, whichever occurred first.

#### Intracranial PFS

Intracranial PFS is defined as the time from randomisation to first documented radiographic evidence of CNS progression. CNS progression is defined as progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions.

#### **4.4.2. Overall survival**

OS is defined as the time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

#### **4.4.3. Objective response**

Objective response is defined as best overall response (CR or PR) across all assessment time-points according to RECIST v1.1, from randomisation until [either \(i\) the end of protocol treatment or \(ii\) the end of follow-up](#).

#### 4.4.4. Toxicity

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

- Adverse events according to CTCAE v5.0 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

#### 4.4.5. Quality of life

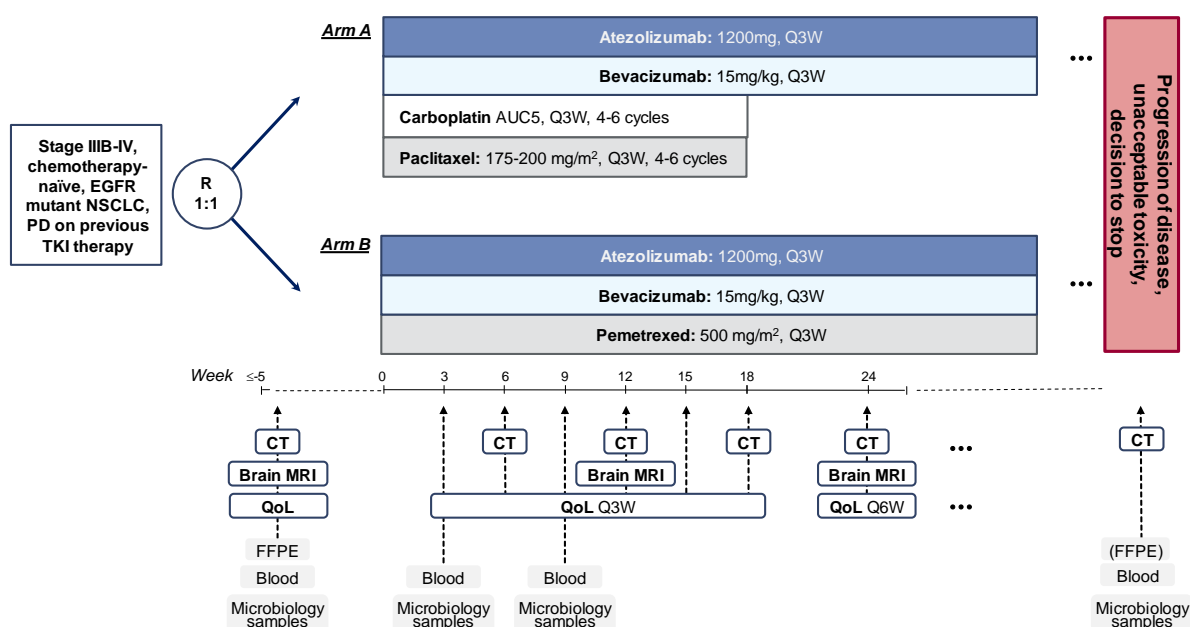
- Quality of life will be assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the lung cancer-specific module (QLQ-LC13).<sup>47,48</sup> The key QoL outcome is the time to deterioration (TTD) in the QLQ-C30 global health status/global QoL.

# TRIAL DESIGN AND DURATION

## 5. Trial design and schema

This is a multinational, multi-centre randomised, open-label, non-comparative phase II study of atezolizumab, bevacizumab and carboplatin plus paclitaxel (Arm A) or atezolizumab, bevacizumab and pemetrexed (Arm B) in patients with stage IIIB-IV NSCLC harbouring EGFR mutations after failure of standard EGFR TKIs.

This is a selection design, randomised trial with two non-comparative parallel arms. Although randomisation will be used to allocate patients to either Arm A or Arm B, the study is not powered or designed to be comparative in nature. The purpose of randomisation is to reduce bias due to patient selection into either treatment arm.



### 5.1. Rationale for trial design

#### 5.1.1. 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 chemotherapy.

To ensure the validity of data 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 (final for efficacy as

well as regular safety interim) in detail will be developed before the corresponding database locks and the beginning of the analyses.

#### 5.1.2. Rationale for PFS as primary endpoint

PFS as an endpoint can reflect tumour growth and can be assessed before the determination of a survival benefit. PFS therefore takes into account both responsive disease as well stable disease. Additionally, in contrast to overall survival, the determination of PFS is not affected by subsequent therapies. Furthermore, with PFS as the primary endpoint, the feasibility of completing the study is increased as a smaller sample size and shorter follow-up is required when compared to conducting a study using overall survival as the endpoint.

#### 5.1.3. 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. 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<sup>49</sup> and available clinical pharmacokinetic, efficacy, and safety data (refer to the *Atezolizumab Investigator's Brochure* and the *Summary of Product Characteristics* for details).

#### 5.1.4. 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 although an OS benefit was shown with 15mg/kg only. 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.

#### 5.1.5. Rationale for combination approach with an immune checkpoint inhibitor and anti-angiogenic agent

Anti-angiogenic agents targeting the VEGF/VEGFR signalling pathway have been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials in non-squamous NSCLC.<sup>17</sup> VEGF production is up-regulated by increased EGFR signalling, via *EGFR* activating mutations, EGFR overexpression and acquired EGFR TKI, further driving

tumour growth and immunosuppression.<sup>18,19,50-52</sup> Taken together, the activity of atezolizumab may be enhanced by the inhibition of VEGF-mediated immunosuppression with bevacizumab. This combination may be more active in *EGFR*-mutant NSCLC and may therefore be an attractive combination approach.<sup>23,45</sup>

#### 5.1.6. Rationale for quality of life assessment

A review<sup>53</sup> on the methodology of quality of life analysis in phase III advanced non-small-cell lung cancer clinical trials showed that the European Organization of Research and Treatment for Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)<sup>47</sup> and its lung cancer-specific module QLQ-LC13<sup>48</sup> were the most frequently used instruments. Further instruments included the Functional Assessment of Cancer Therapy-Lung (FACT-L)<sup>54,55</sup> and the Lung Cancer Symptom Scale (LCSS).<sup>56</sup>

The QLQ-C30 in combination with the QLQ-LC13 is rather long, especially, if considering frequent assessments. Nevertheless the QLQ-C30/LC13 will be used in this trial in order to be able to interpret the results in light of those gained in the IMpower150 trial. As there is no formal comparison planned for the two arms, the QoL profiles over time are more important than changes from baseline to a specific time point. This, however, requires relatively frequent QoL assessments. With short intervals between QoL assessments the time to QoL deterioration (TTD) is considered the best approach for longitudinal analysis.<sup>57</sup> Therefore the time to deterioration in the EORTC QLQ-C30 is the key QoL outcome.

## 6. Sample size and trial duration

A total of 95 randomised patients are needed (for details regarding sample size calculation see Section 16). The patients will be recruited from approximately 25 sites in seven countries.

Clinical visits (until the timepoint of primary analysis) are expected to span approximately 24 months after randomisation of the first patient, assuming an accrual rate of 1-2 patients per months during the first 6 months as the trial is activated by the participating centres and 12-15 patients per month thereafter (total accrual time of 12 months) plus 12 months of follow-up for all randomized patients. The duration of individual patients' trial participation is anticipated to be between 1 and 2 years.

The primary analysis will be available approximately 2.5 years after the inclusion of the first patient, that is 6 months after the last randomized patient has completed 12 months of follow-up.

# 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. Patients (male/female) must be  $\geq 18$  years of age.

7.1.2. Chemotherapy naïve, non-squamous NSCLC, stage IIIB/C (not amenable to radical therapy) or stage IV according to 8th TNM classification. Patients who have received previous adjuvant or neoadjuvant chemotherapy are eligible if the date of last dose of treatment was at least 12 months before randomisation

7.1.3. Known *EGFR* mutations genotypes by tissue or ctDNA; patients with common mutations (L858R or Del19) and other rare mutations (e.g. S768I, G719X) are eligible

7.1.4. Measurable or evaluable disease as defined by RECIST v1.1

7.1.5. Disease progression (during or after) or unacceptable side effects from prior treatment with at least one EGFR TKI (washout period = 7 days).

If most recent line of treatment (1<sup>st</sup> or 2<sup>nd</sup> line) was a third-generation EGFR TKI (e.g. osimertinib):

- Patient must be known to be *EGFR* mutation positive, either on fresh tumour biopsy taken  $>7$  days prior to protocol treatment start or by recent ctDNA analysis (informative ctDNA test, local test).
- T790M genotype is allowed

If most recent line of treatment (1<sup>st</sup> or 2<sup>nd</sup> line) was a first- or second-generation EGFR TKI (e.g. afatinib, dacomitinib, erlotinib, gefitinib):

- Patient must be known to be tissue EGFR T790M wild type (local test) on most recent line of EGFR TKI or if no tissue re-biopsy, no evidence of T790M on ctDNA but identified L858R, del19, S768I or G719X genotypes (informative ctDNA test, local test)

7.1.6. Treatment with an EGFR TKI therapy for at least 30 days

7.1.7. Adequate haematological function:

- Haemoglobin  $\geq 90$  g/L

- Absolute neutrophils count (ANC)  $\geq 1.5 \times 10^9/\text{L}$
- Platelet count  $\geq 100 \times 10^9/\text{L}$

7.1.8. Adequate renal function:

- Creatinine clearance  $\geq 45 \text{ mL/min}$  (using the Cockcroft-Gault formula below):

Cockcroft-Gault formula

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

7.1.9. Adequate liver function:

- ALT and AST  $\leq 2.5 \times \text{ULN}$ . If the patient has liver metastases, ALT and AST must be  $\leq 5 \times \text{ULN}$
- Total bilirubin  $\leq 1.5 \times \text{ULN}$ . If the patient has documented Gilbert's syndrome (unconjugated hyperbilirubinaemia)  $\leq 3 \times \text{ULN}$ .

7.1.10. Willingness to provide any surplus tumour sample obtained at the time of acquired resistance to prior EGFR TKI

7.1.11. Men and women of childbearing potential must agree to use adequate contraception

7.1.12. Eastern Cooperative Oncology Group (ECOG) performance status 0-1

7.1.13. Life expectancy  $\geq 12$  weeks

7.1.14. Women of childbearing potential, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before randomisation.

7.1.15. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations including follow up.

## 7.2. Exclusion criteria

7.2.1. Prior systemic cytotoxic chemotherapy for advanced stage NSCLC.

Patients who had received previous adjuvant or neoadjuvant chemotherapy are eligible if the last dose of treatment was at least 12 months before randomisation.

7.2.2. Prior therapy with bevacizumab or other anti-angiogenic agent

- 7.2.3. Prior immune checkpoint inhibitor therapy
- 7.2.4. More than two lines of EGFR TKI therapy
- 7.2.5. Known small-cell lung carcinoma (SCLC) or high grade neuroendocrine carcinoma (if progression biopsy has been performed locally).
- 7.2.6. Squamous cell histologic subtype
- 7.2.7. Known EGFR T790M positive genotype by tissue on most recent EGFR TKI progression or ctDNA **and have not received** an approved EGFR TKI targeting T790M (e.g. a third-generation EGFR TKI such as osimertinib).
- 7.2.8. Active or untreated CNS metastases as determined by brain MRI
  - Patients with CNS metastases must be non-progressive by RECIST v1.1 and symptomatically stable with no ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
- 7.2.9. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of randomization.
- 7.2.10. Presence or history of a malignant disease that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
- 7.2.11. Clear tumour infiltration into the thoracic great vessels (seen on imaging)
- 7.2.12. QTc of grade  $\geq 3$  according to CTCAE v5.0
- 7.2.13. Active autoimmune disease that has required systemic treatment in past 2 years. Patients with vitiligo, controlled type I diabetes mellitus on stable insulin, or residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment are permitted
- 7.2.14. Active or uncontrolled HIV, tuberculosis, hepatitis B or C infection
- 7.2.15. Live attenuated vaccination within 4 weeks prior to randomisation.

- 7.2.16. Subject receiving any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, or tocilizumab) [within 6 weeks prior to treatment start](#).
- 7.2.17. History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
- 7.2.18. Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg)
- Anti-hypertensive therapy to achieve these parameters is allowable.
- 7.2.19. Prior history of hypertensive crisis or hypertensive encephalopathy
- 7.2.20. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization
- 7.2.21. History of haemoptysis ( $\geq 2.5$  mL of bright red blood per episode) within 1 month prior to randomization
- 7.2.22. Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation)
- 7.2.23. Current or recent (within 10 days before randomization) use of aspirin (>325 mg/day) or treatment with dipyridamole, ticlopidine, clopidogrel, and clostazol
- 7.2.24. 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 randomization
- The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to randomization.
  - Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR  $< 1.5 \times$  ULN and aPTT is within normal limits within 14 days prior to randomization.
  - Prophylactic use of low-molecular-weight heparin (i.e., enoxaparin 40 mg/day) is permitted.
- 7.2.25. 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 within 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.

7.2.26. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to randomization

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

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

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

7.2.30. Proteinuria, as demonstrated by urine dipstick or >1.0 g of protein in a 24-hour urine collection

- All patients with  $\geq 2+$  protein on dipstick urine analysis at baseline must undergo a 24-hour urine collection and must demonstrate  $\leq 1$  g of protein in 24 hours.

7.2.31. Any unresolved toxicities from prior therapy greater than CTCAE v5.0 grade 1 at the time of starting trial treatment with the exception of alopecia

7.2.32. History of hypersensitivity to the known active substances (atezolizumab, bevacizumab and chemotherapy drugs) or to any of the excipients.

7.2.33. History of hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.

7.2.34. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

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

7.2.36. 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 trial treatment

7.2.37. History of active diverticulitis

## 8. Method of treatment assignment

This is a randomised, open-label phase II 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: atezolizumab, bevacizumab and carboplatin plus paclitaxel (Arm A) or atezolizumab, bevacizumab and pemetrexed (Arm B). Block stratified randomisation (with blocks of random size, multiples of two) will be performed centrally and will be balanced by institution.

The stratification factor is: prior third-generation TKI (e.g. osimertinib) versus no prior third-generation TKI.

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

## 9. Protocol treatment and other treatments relevant to the trial

F. Hoffmann-La Roche will provide atezolizumab and bevacizumab free of charge. The protocol specified chemotherapy regimens (carboplatin plus paclitaxel or pemetrexed) will be sourced by the sponsor (ETOP).

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

### 9.1. Overview protocol treatment

#### Arm A:

- Atezolizumab (1200 mg) Q3W, until PD\*
- Bevacizumab (15 mg/kg), Q3W, until PD
- Carboplatin (AUC5) Q3W, 4-6 cycles
- Paclitaxel<sup>‡</sup> (175-200 mg/m<sup>2</sup>, at the investigator's discretion), Q3W, 4-6 cycles

#### Arm B:

- Atezolizumab (1200 mg), Q3W, until PD\*
- Bevacizumab (15 mg/kg), Q3W, until PD
- Pemetrexed (500 mg/m<sup>2</sup>), Q3W, until PD

\*Atezolizumab treatment beyond RECIST v1.1-defined progression will be allowed if patient is continuing to derive clinical benefit.

<sup>‡</sup>[Asian population](#): Due to increased haematological toxicities observed in Asian patients in the IMpower150 trial, it is recommended that the starting dose of paclitaxel should be 175 mg/m<sup>2</sup> every three weeks.

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).

Treatment will continue until disease progression, toxicity, or patient/physician decision.

[Patients should receive anti-emetics according to the local standard of care and manufacturer's instruction. Corticosteroids as a premedication for chemotherapy is permitted and is dosed according to local practice.](#)

## **9.2. Atezolizumab**

Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week ( $\pm 3$  days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST v1.1-defined progression will be allowed if patient is continuing to derive clinical benefit

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

Supplies will be provided free of charge by F. Hoffmann-La Roche Ltd. For details please refer to the *ABC-lung Drug Supply Manual*.

## **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 ( $\pm 3$  days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

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

Supplies will be provided free of charge by F. Hoffmann-La Roche Ltd. For details please refer to the *ABC-lung Drug Supply Manual*.

## 9.4. Chemotherapy

### 9.4.1. Carboplatin and paclitaxel

Patients in treatment Arm A will receive carboplatin, AUC5 plus paclitaxel, 175-200 mg/m<sup>2</sup>, at the investigator's discretion, every 3 weeks for 4-6 cycles.

Asian population: Due to increased haematological toxicities observed in Asian patients in the IMpower150 trial, it is recommended that the starting dose of paclitaxel should be 175 mg/m<sup>2</sup> every three weeks.

### 9.4.2. Pemetrexed

Patients in treatment Arm B will receive Pemetrexed, 500 mg/m<sup>2</sup> every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Please note that premedication with folic acid and vitamin B12 must be given according to the pemetrexed Summary of Product Characteristics.

### 9.4.3. Dose modification and delay criteria for chemotherapy

Dose modification, reductions and holds for carboplatin, paclitaxel and pemetrexed should be **performed according to local guidelines**. Please refer to the respective *Summaries of Product Characteristics*.

## 9.5. Packaging and labelling

Supplies will be affixed with a clinical trial label. Drug labels will comply with the legal requirements as applicable and will be printed in the local language.

### 9.5.1. 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.

### 9.5.2. 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 *ABC-lung Drug Supply Manual* for complete details.

## 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 the protocol 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/or the patient has discontinued protocol treatment. Prohibited concomitant therapies include, but are not limited to, chemotherapy (other than carboplatin, paclitaxel 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, **as well as denosumab and zoledronic acid for the treatment of bone metastases, are allowed.**
- Live attenuated 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 **6 weeks** 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**.
- The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. [Systemic corticosteroids can be used as a premedication](#). Systemic corticosteroids or other immunosuppressants can be used to treat immune-mediated adverse reactions after starting 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 least 6 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 RECIST v1.1
- Treatment with atezolizumab beyond PD is allowed if patient is continuing to derive clinical benefit
- Unacceptable toxicity to protocol treatment
  - Medical condition that prevents further treatment
  - Patient withdraws consent
  - Patient becomes pregnant

## 10. Tumour response evaluation

### 10.1. CT schedule for response evaluation

Radiological tumour assessment by CT scans of thorax / upper abdomen (from top of thorax until adrenal glands and full liver and kidney included) as well as a brain MRI will be done at baseline before randomisation.

CT scans will be repeated every 6 weeks ( $\pm 4$  days) for 18 months and then every 12 weeks ( $\pm 2$  weeks) from randomisation until progression of disease determined according to RECIST v1.1 or until the end of the trial, whatever is first. The same imaging technique, acquisition, and processing parameters should be used in a patient throughout the trial.

Brain MRI will be repeated every 12 weeks ( $\pm 2$  weeks) from randomisation until progression of disease determined according to RECIST v1.1.

**For the readout of the primary endpoint (PFS at 12 months), it is important that all patients (without progression up to 12 months) will have a CT scan and brain MRI between week 52 and week 54 after randomisation.**

### 10.2. Storage of images

All CT images and MRI scans must be stored locally in electronic format for potential central review, please consult the *ABC-lung Procedures Manual* for details.

### 10.3. Response evaluation criteria in solid tumours (RECIST version 1.1)

#### 10.3.1. Introduction

All included patients will be evaluated for disease response and progression according to the revised response evaluation criteria in solid tumours (RECIST v1.1).<sup>45</sup>

#### 10.3.2. 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  $\leq 5$  mm contiguous reconstruction algorithm. 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  $\geq 10$  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 foreseen for regular 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.

### 10.3.3. Measurable disease

Measurable disease is defined as the presence of at least one measurable lesion.

Measurable lesions:

- Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray

**Reminder:** A lesion in a previously irradiated area is not eligible for measurable disease.

- **Malignant lymph nodes:** to be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan, assuming the slice thickness is  $\leq 5$  mm. At baseline and in follow-up, only the short axis will be measured.

### 10.3.4. Non-measurable disease

Non-measurable disease is defined as lesions or sites of disease that cannot be measured. 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  $\geq 10$  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 locoregional 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

#### 10.3.5. Selection of target lesions

Target lesions should be identified, measured and recorded at baseline. At baseline, there can be up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ. Target lesions should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. **Lymph nodes** selected as target lesions should always have the **short axis** recorded. All **other lesions** should always have their **longest diameters** recorded. The sum of diameters will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

#### 10.3.6. Selection of non-target lesions

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

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

#### 10.3.7. Evaluation of target lesions

All target lesions will be measured at each tumour assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- **Complete Response (CR):** Disappearance of all target lesions. 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):** At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters.
- **Progression (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions (see section 10.3.9) denotes disease progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

**Note:** All target lesions, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a target lesion is thought likely to have disappeared, use "0 mm."

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

#### 10.3.8. Evaluation of non-target lesions

- **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).
- **Progression (PD):** 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.

When no imaging is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesions are evaluated at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

#### 10.3.9. 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 patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan when the lesion was discovered.

Lesions or sites of disease found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions. The detection of new lesions is not restricted to the examination methods used at baseline.

**Note:** the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

#### 10.3.10. Additional considerations

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

#### 10.3.11. Determination of time point 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 the table below.

### 10.3.12. For patients with measurable disease

**Table 1: Measurable Disease - Overall Response**

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.

### 10.3.13. For patients with non-measurable disease

**Table 2: Non-measurable Disease - Overall Response**

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR / non-PD*	No	Non-CR / non-PD*
Not 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.

### 10.3.14. Determination of best overall response

Best overall response is defined as best response recorded from the start of treatment across all time points until disease progression. Confirmation of partial or complete response by an additional scan is not requested in this trial.

## 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) as well as brain MRIs will be done as indicated in Section 10.1 until progression of disease.

### 11.2. Quality of life

Quality of life assessments will be done at screening and then [within 3 days before treatment administration](#) of cycles 2-7 (e.g. at weeks 3, 6, 9, 12, 15 and 18) and thereafter every 6 weeks up to 12 months or until disease progression, whatever is first.

### 11.3. Screening

#### 11.3.1. Written informed consent:

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

The following evaluations should be done within 5 weeks before randomisation. If examinations were done prior to 5 weeks before randomisation, they have to be repeated

#### 11.3.2. Demographics

Year of birth, gender, race

#### 11.3.3. Medical history

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

#### 11.3.4. Vital signs:

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

#### 11.3.5. Thyroid function

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

#### 11.3.6. HIV and hepatitis B and C status

#### 11.3.7. Quality of life assessment (before randomisation)

#### 11.3.8. 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 7 days before randomisation. Pregnancy testing has to be repeated throughout protocol trial treatment according to local standards.

#### 11.3.9. Chemistry

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

#### 11.3.10. Haematology

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

#### 11.3.11. Coagulation profile (INR)

#### 11.3.12. Liver function test

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

#### 11.3.13. Renal function test

Urea, uric acid, serum creatinine and creatinine clearance calculated according to Cockcroft-Gault (see Section 7.1.6).

#### 11.3.14. Urine analysis

On first morning urine sample: pH, specific gravity, glucose, protein, ketones and blood (dipstick permitted), elements and microscopic examination if needed. [Patients with urine dipstick reading for protein 2+ or higher should undergo further assessment with a 24-hour urine collection.](#)

#### 11.3.15. Brain MRI, performed within 5 weeks before randomisation.

#### 11.3.16. 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.

#### 11.3.17. TNM categories (8<sup>th</sup> edition)

#### 11.3.18. Pathology report

A copy of the pathology report, including the results from EGFR mutation testing, 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)

#### 11.3.19. FFPE tumour material for translational research

FFPE tumour material from a biopsy sample (obtained at the time of acquired resistance to prior EGFR TKI), taken >7 days prior to protocol treatment start must be submitted.

#### 11.3.20. Blood samples for translational research (see Section 12.2.2 for details).

Blood samples at baseline 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 first treatment administration in cycle 1.

#### 11.3.21. Oropharyngeal swabs and faecal samples for microbiome analysis (see Section 12.2.3 for details)

### 11.4. Evaluations during protocol treatment period

#### At each treatment cycle:

The following evaluations have to be done at every treatment 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 and concomitant medications

##### 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 7.1.6).

#### 11.4.8. Quality of life

Within 3 days before treatment administration in cycles 2-7 (e.g. at weeks 3, 6, 9, 12, 15 and 18) and thereafter every 6 weeks up to 12 months or until disease progression, 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), elements and microscopic examination if needed. 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 2 and at treatment cycle 4

The following additional evaluation has to be done at cycles 2 and 4, within 3 days before treatment administration:

#### 11.4.11. Blood sample for translational research (see Section 0 for details):

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

#### 11.4.12. Oropharyngeal swabs and faecal samples for microbiome analysis (see Section 12.2.3 for details)

#### At every 4<sup>th</sup> treatment cycle

The following additional evaluation has to be done at every 4th treatment cycle, within 3 days before treatment administration:

#### 11.4.13. Thyroid function

TSH, free T3 (or total T3 if free T3 is not performed per local standards), and free T4, for as long as the patient is receiving atezolizumab.

## **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.

### **11.5.3. Oropharyngeal swabs and faecal samples for microbiome analysis (see Section 12.2.3 for details)**

## **11.6. Evaluations at the end of treatment visit**

Patients are considered to be on protocol treatment for as long as they receive either atezolizumab, bevacizumab and/or chemotherapy. 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 and concomitant medications**

### **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 7.1.6).

11.6.7. Radiological tumour assessment (CT-scan and MRI) has to be repeated if not done within [the indicated timeline \(see Section 10.1\)](#), 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 12 weeks ( $\pm 2$  weeks), 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. Quality of life assessment (according to schedule indicated in Section 11.2)

#### 11.7.3. 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) and brain MRIs according to the schedule indicated in Section 11.1.

### **11.8. Evaluations in the follow-up phase beyond progression**

Patients with progression that ends trial treatment will be followed up every 12 weeks ( $\pm 2$  weeks) starting from date of progression until trial end (e.g. until approximately 12 months after inclusion of the last patient). 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 created with centralised samples for translational research, integral to the trial. The required pathological material (described below) is submitted to, catalogued, and maintained at two Central Laboratories: Tumour tissue blocks and blood samples will be centrally collected and biobanked at the **Center of Experimental Therapeutics (CTE), CHUV – Department of Oncology, Lausanne, Switzerland.**

Microbiological samples will be biobanked at the **Imperial College London, United Kingdom.** This would allow investigation of changes in the lung microbiome.

The material will be centrally archived and subjected to central histology review and biomarker testing. Oropharyngeal swabs would allow investigation of changes in the lung microbiome. Eventually, the biological material will be made available for translational research, following completion of the primary trial translational research objectives.

### 12.2. Collected biological samples

#### 12.2.1. FFPE-material

FFPE tumour tissue (obtained at the time of acquired resistance to prior EGFR TKI) 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.
- A tumour re-biopsy at the time of progression is strongly recommended. An FFPE tumour tissue block or slides should be submitted.
- Cytological specimens are accepted in this trial.

### 12.2.2. Blood and serum samples

#### At baseline

Blood samples at baseline 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 first treatment administration in cycle 1.

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

#### At cycle 2, within 3 days before treatment administration

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

#### At cycle 4, within 3 days before treatment administration

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

#### At disease progression

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

Blood samples must be immediately frozen at -80°C.

### 12.2.3. Microbiological samples

Human and oral microbiomes and their various communities of microorganisms play important roles in regulating host functions. Preclinical studies provide evidence that microbiota may enhance cancer development in response to the host's ever-changing internal and environmental factors.<sup>58</sup>

The lung microbiome is now a well-established feature and preliminary microbiome analyses have indicated some changes in general which include pathogens that are significantly associated with lung cancer.<sup>59</sup> Thus, specific microbial changes could represent specific biomarkers for lung cancer.

- Oropharyngeal swabs will be taken to investigate the lung microbiome. [Oropharyngeal swabs will be taken at baseline, at cycle 2 and 4 \(within 3 days before treatment administration\), and at disease progression.](#)
- Faecal samples will be taken to investigate microorganisms in the gut. [Faecal samples will be taken at baseline, at cycle 2 and 4 \(within 3 days before treatment administration\), and at disease progression.](#)

Oropharyngeal swabs and faecal samples must be immediately frozen at -80°C at participating sites.

If it is not possible for the patient to provide a faecal sample when in the clinic, the patient would need to collect the faecal sample at home [using the provided collection kit, and bring it with them to their next hospital visit. The procedures manual further describes all steps.](#)

Oropharyngeal swabs will be centrally collected and biobanked at the Imperial College, London, United Kingdom.

Critical for all microbiome non-culture studies is freezing post sampling as this prevent bacterial growth or death altering the proportion of different bacteria present. As a consequence it is invariably more practical for sampling to be done in the clinical setting whenever possible.

#### 12.2.4. Submission of biological material

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, [blood samples, oropharyngeal swabs and faecal samples](#) will be shipped to the central reference laboratory in Lausanne. Oropharyngeal swabs and faecal samples will then be further shipped to the central reference laboratory in London (refer to location below).

#### 12.2.5. Submission of FFPE material

- FFPE tumour material as defined in Section 12.2.1. 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 >7 days 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, [especially if it is needed for patient care](#), blocks can be returned to the submitting site. [The majority of the planned central analyses is done towards end of the study, and it is thus important to keep the blocks at ETOP as long as possible to ensure high quality analysis.](#)

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

FFPE 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

#### 12.2.6. Submission of blood samples

For blood collection and serum preparation see *ABC-lung Procedures Manual*.

Blood samples must be stored locally at -80°C and will be kept at the participating site until the end of the study. One single shipment will be arranged by ETOP, when all blood samples are collected of all patients.

#### 12.2.7. Submission of microbiological samples

For oropharyngeal swabs and faecal samples handling see *ABC-lung Procedures Manual*.

Oropharyngeal swabs and faecal samples must be stored locally at -80°C and will be kept at the participating site until the end of the study. Shipments will be organized as one single shipment.

## 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 15-19 ABC-lung 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

Patients are considered to be on protocol treatment for as long as they receive either atezolizumab, bevacizumab of chemotherapy and until one of the following events occurs:

- Disease progression according to the RECIST v1.1. (treatment with atezolizumab beyond PD is allowed if patient is continuing to derive clinical benefit)
- 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. The level of withdrawal (e.g. whether the patient agrees to continue follow-up visits or allows the collection of further information from medical records or publicly available registries) should be documented in the *withdrawal of consent form* and in the eCRF, according to the instructions in the *ABC-lung CRF Completion Guidelines*.

For the patient's safety, an end of treatment visit should be performed.

# 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 ABC-lung 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 14.20).

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 Section 14.2.5.

### 14.1. Risks associated with atezolizumab

Atezolizumab has been associated with risks such as infusion-related reaction and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis and [Severe Cutaneous Adverse Reactions \(SCARs\)](#). 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:

Exception: Atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks 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 Affairs. The investigator and the ETOP Medical Affairs will determine the acceptable length of treatment interruption.

#### 14.1.2. Management guidelines for 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 3 for the management guidelines for pulmonary events.

**Table 3: Management guidelines for pulmonary events, including pneumonitis**

Event	Management
Grade 1	<ul style="list-style-type: none"> <li>• Continue atezolizumab and monitor closely.</li> <li>• Re-evaluate on serial imaging.</li> <li>• Consider patient referral to pulmonary specialist.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage.</li> <li>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>• For recurrent events, treat as a grade 3 or 4 event.</li> </ul>
Grade 3 or 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>• Bronchoscopy or bronchoscopic alveolar lavage is recommended.</li> <li>• Initiate treatment with 1–2 mg/kg/day i.v. prednisone or equivalent.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.</li> </ul>

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@ibcs.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 4.

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 4: 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	<b>All events:</b> Monitor liver function tests more frequently until return to baseline values. <b>Events of &gt;5 days' duration:</b> <ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 3 or 4	<ul style="list-style-type: none"> <li>Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish aetiology of hepatic injury.</li> <li>Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.</li> </ul>

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@ibcs.org).

### Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhoea or colitis are provided in Table 5.

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 5: Management guidelines for gastrointestinal events (diarrhoea or colitis)**

Event	Management
Grade 1	<ul style="list-style-type: none"> <li>Continue atezolizumab.</li> <li>Initiate symptomatic treatment.</li> <li>Endoscopy is recommended if symptoms persist for &gt;7 days.</li> <li>Monitor closely.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>Initiate symptomatic treatment.</li> <li>Patient referral to GI specialist is recommended.</li> <li>For recurrent events or events that persist &gt;5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>Refer patient to GI specialist for evaluation and confirmatory biopsy.</li> <li>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.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>Refer patient to GI specialist for evaluation and confirmation biopsy.</li> <li>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.</li> <li>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>If event resolves to grade 1 or better, taper corticosteroids over <math>\geq 1</math> month</li> </ul>

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  $\leq 10$  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  $\geq 1$  month to  $\leq 10$  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@ibcs.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 6.

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, adrenocorticotrophic 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 6: Management guidelines for endocrine events**

<b>Event</b>	<b>Management</b>
Asymptomatic hypothyroidism	<ul style="list-style-type: none"><li>• Continue atezolizumab.</li><li>• Initiate treatment with thyroid replacement hormone.</li><li>• Monitor TSH weekly.</li></ul>
Symptomatic hypothyroidism	<ul style="list-style-type: none"><li>• Withhold atezolizumab.</li><li>• Initiate treatment with thyroid replacement hormone.</li><li>• Monitor TSH weekly.</li><li>• Consider patient referral to endocrinologist.</li><li>• Resume atezolizumab when symptoms are controlled and thyroid function is improving.</li></ul>
Asymptomatic hyperthyroidism	<b>TSH <math>\geq 0.1</math> mU/L and <math>&lt; 0.5</math> mU/L:</b> <ul style="list-style-type: none"><li>• Continue atezolizumab.</li><li>• Monitor TSH every 4 weeks.</li></ul> <b>TSH <math>&lt; 0.1</math> mU/L:</b> <ul style="list-style-type: none"><li>• Follow guidelines for symptomatic hyperthyroidism.</li></ul>
Symptomatic hyperthyroidism	<ul style="list-style-type: none"><li>• Withhold atezolizumab.</li><li>• Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.</li><li>• Consider patient referral to endocrinologist.</li><li>• Resume atezolizumab when symptoms are controlled and thyroid function is improving.</li><li>• permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li></ul>

<b>Symptomatic adrenal insufficiency</b>	
Grade 2-4	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform appropriate imaging.</li> <li>• 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.</li> <li>• If event resolves to grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.<sup>b</sup></li> <li>• 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.<sup>c</sup></li> </ul>
<b>Hyperglycaemia</b>	
Grade 1 or 2	<ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• 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.</li> <li>• Monitor for glucose control.</li> </ul>
Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold atezolizumab.</li> <li>• Initiate treatment with insulin.</li> <li>• Monitor for glucose control.</li> <li>• Resume atezolizumab when symptoms resolve and glucose levels are stable.</li> </ul>
<b>Hypophysitis (pan-hypopituitarism)</b>	
Grade 2 or 3	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to endocrinologist.</li> <li>• Perform brain MRI (pituitary protocol).</li> <li>• 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.</li> <li>• Initiate hormone replacement if clinically indicated.</li> <li>• If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>• For recurrent hypophysitis, treat as a grade 4 event.</li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.</li> <li>• Refer patient to endocrinologist.</li> <li>• Perform brain MRI (pituitary protocol).</li> <li>• 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.</li> <li>• Initiate hormone replacement therapy if clinically indicated.</li> </ul>

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- 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  $\leq 10$  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  $\geq 1$  month to  $\leq 10$  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@ibcs.org).

## Ocular events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 7.

**Table 7: Management guidelines for ocular events**

Event	Management
Grade 1	<ul style="list-style-type: none"> <li>Continue atezolizumab.</li> <li>Patient referral to ophthalmologist is strongly recommended.</li> <li>Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.</li> <li>If symptoms persist, treat as a grade 2 event.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>Patient referral to ophthalmologist is strongly recommended.</li> <li>Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 3 or 4	<ul style="list-style-type: none"> <li>Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>Refer patient to ophthalmologist.</li> <li>Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.</li> <li>If event resolves to grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> </ul>

- 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  $\leq 10$  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  $\geq 1$  month to  $\leq 10$  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@ibcs.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 8.

**Table 8: Management guidelines for immune-mediated myocarditis**

Event	Management
Grade 1	<ul style="list-style-type: none"><li>• Continue atezolizumab.</li></ul>
Grade 2	<ul style="list-style-type: none"><li>• Withhold atezolizumab for up to 12 weeks after event onset<sup>a</sup> contact ETOP Medical Affairs.</li><li>• Refer patient to cardiologist.</li><li>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation, or ventricular assist device as appropriate.</li><li>• 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.<sup>a</sup></li><li>• If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li><li>• If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li></ul>
Grade 3-4	<ul style="list-style-type: none"><li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li><li>• Refer patient to cardiologist.</li><li>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation, or ventricular assist device as appropriate.</li><li>• 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.<sup>a,b</sup></li><li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li><li>• If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.</li></ul>

Event	Management
	<p>a. Atezolizumab may be withheld for a longer period of time (i.e., &gt;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.</p> <p>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.</p> <p>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@ibcs.org).</p>

### 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.<sup>60</sup> 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),<sup>61-63</sup> 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 9.

**Table 9: Management guidelines for infusion-related reactions and cytokine-release syndrome**

Event	Management
<p>Grade 1<sup>a</sup></p> <p>Fever<sup>b</sup> with or without constitutional symptoms</p>	<ul style="list-style-type: none"> <li>• Immediately interrupt infusion.</li> <li>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.</li> <li>• If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.</li> <li>• If symptoms recur, discontinue infusion of this dose.</li> <li>• Administer symptomatic treatment,<sup>c</sup> including maintenance of IV fluids for hydration.</li> <li>• In case of rapid decline or prolonged cytokine-release syndrome (&gt;2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per grade 2.</li> <li>• 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.</li> </ul>
<p>Grade 2<sup>a</sup></p> <p>Fever<sup>b</sup> with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen<sup>d</sup> by nasal cannula or blow-by</p>	<ul style="list-style-type: none"> <li>• Immediately interrupt infusion.</li> <li>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.</li> <li>• If symptoms recur, discontinue infusion of this dose.</li> <li>• Administer symptomatic treatment.<sup>c</sup></li> <li>• For hypotension, administer IV fluid bolus as needed.</li> <li>• 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.</li> <li>• 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.</li> <li>• Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).</li> <li>• Consider anti-cytokine therapy.<sup>e</sup></li> <li>• 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.</li> <li>• 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.</li> <li>• If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the ETOP Medical Affairs.</li> </ul>

Event	Management
<p>Grade 3<sup>a</sup></p> <p>Fever<sup>b</sup> with hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen<sup>d</sup> by nasal cannula, face mask, non-rebreather mask, or venturi mask</p>	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact the ETOP Medical Affairs.<sup>f</sup></li> <li>• Administer symptomatic treatment.<sup>c</sup></li> <li>• 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.</li> <li>• 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.</li> <li>• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).</li> <li>• Consider anti-cytokine therapy.<sup>e</sup></li> <li>• 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.</li> </ul>
<p>Grade 4<sup>a</sup></p> <p>Fever<sup>b</sup> with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)</p>	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact the ETOP Medical Affairs.<sup>f</sup></li> <li>• Administer symptomatic treatment.<sup>c</sup></li> <li>• 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.</li> <li>• 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.</li> <li>• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).</li> <li>• Consider anti-cytokine therapy.<sup>e</sup> For patients who are refractory to anti-cytokine therapy, experimental treatments<sup>g</sup> may be considered at the discretion of the investigator and in consultation with the ETOP Medical Affairs.</li> <li>• Hospitalize patient until complete resolution of symptoms.</li> </ul>

Event	Management
<p>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 <b>Adverse Events eCRF</b>. Organ toxicities associated with cytokine-release syndrome should not influence overall cytokine-release syndrome grading.</p> <p>b. Fever is defined as temperature <math>\geq 38^{\circ}\text{C}</math> 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.</p> <p>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.</p> <p>d. Low flow is defined as oxygen delivered at <math>\leq 6</math> L/min, and high flow is defined as oxygen delivered at <math>&gt; 6</math> L/min.</p> <p>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.<sup>61-63</sup></p> <p>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.</p> <p>g. Refer to Riegler et al. (2019) for information on experimental treatments for cytokine-release syndrome.<sup>64</sup></p>	

### 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 10.

**Table 10: Management guidelines for pancreatic events, including pancreatitis**

Event	Management
Amylase and/or lipase elevation	
Grade 2	<p><u>Amylase and/or lipase <math>&gt; 1.5\text{-}2.0 \times \text{ULN}</math>:</u></p> <ul style="list-style-type: none"> <li>• Continue atezolizumab.</li> <li>• Monitor amylase and lipase weekly.</li> <li>• For prolonged elevation (e.g., <math>&gt; 3</math> weeks), consider treatment with 10 mg/day oral prednisone or equivalent.</li> </ul> <p><u>Asymptomatic with amylase and/or lipase <math>&gt; 2.0\text{-}5.0 \times \text{ULN}</math>:</u></p> <ul style="list-style-type: none"> <li>• Treat as grade 3 event</li> </ul>

Event	Management
Grade 3 or 4	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to GI specialist.</li> <li>• Monitor amylase and lipase every other day.</li> <li>• If no improvement, consider treatment with 1-2 mg/kg/day oral prednisone or equivalent.</li> <li>• If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>• For recurrent events, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
<b>Immune-mediated pancreatitis</b>	
Grade 2 or 3	<ul style="list-style-type: none"> <li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>• Refer patient to GI specialist.</li> <li>• 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.</li> <li>• If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>• If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>• For recurrent events, permanently discontinue atezolizumab and ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>• Refer patient to GI specialist.</li> <li>• 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.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.</li> </ul>

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@ibcs.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 11.

**Table 11: Management guidelines for dermatologic events**

Event	Management
Grade 1	<ul style="list-style-type: none"> <li>Continue atezolizumab.</li> <li>Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Continue atezolizumab.</li> <li>Consider patient referral to dermatologist for evaluation and, if indicated, biopsy.</li> <li>Initiate treatment with topical corticosteroids.</li> <li>Consider treatment with higher-potency topical corticosteroids if event does not improve.</li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>Consider patient referral to dermatologist for evaluation and, if indicated, biopsy.</li> <li>Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Stevens-Johnson syndrome or toxic epidermal necrolysis	<p>Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:</p> <ul style="list-style-type: none"> <li>Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.</li> <li>Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy.</li> <li>Follow the applicable treatment and management guidelines above.</li> <li>If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.</li> </ul>

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@ibcs.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 12.

**Table 12: Management guidelines for neurologic disorders**

Event	Management
<b>Immune-mediated neuropathy</b>	
Grade 1	<ul style="list-style-type: none"><li>• Continue atezolizumab.</li><li>• Investigate aetiology.</li></ul>
Grade 2	<ul style="list-style-type: none"><li>• Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li><li>• Investigate aetiology.</li><li>• Initiate treatment as per institutional guidelines.</li><li>• If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li><li>• If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li></ul>
Grade 3 or 4	<ul style="list-style-type: none"><li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li><li>• Initiate treatment as per institutional guidelines.</li></ul>
Myasthenia gravis and Guillain-Barré syndrome (any grade)	<ul style="list-style-type: none"><li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li><li>• Refer patient to neurologist.</li><li>• Initiate treatment as per institutional guidelines.</li><li>• Consider initiation of 1-2 mg/kg/day oral or i.v. prednisone or equivalent.</li></ul>

- 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  $\leq 10$  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  $\geq 1$  month to  $\leq 10$  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@ibcs.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 13.

**Table 13: Management guidelines for immune-mediated meningoencephalitis**

Event	Management
All grades	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs<sup>a</sup></li> <li>• Refer patient to neurologist.</li> <li>• 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.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to Grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> </ul>

- 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@ibcs.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 14.

**Table 14: Management guidelines for renal events**

Event	Management
Grade 1	<ul style="list-style-type: none"> <li>Continue atezolizumab.</li> <li>Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset.<sup>a</sup></li> <li>Refer patient to renal specialist.</li> <li>Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 3 or 4	<ul style="list-style-type: none"> <li>Permanently discontinue atezolizumab and contact the ETOP Medical Affairs.</li> <li>Refer patient to renal specialist and consider renal biopsy.</li> <li>Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.</li> <li>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>If event resolves to grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> </ul>

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  $\leq 10$  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  $\geq 1$  month to  $\leq 10$  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. Management guidelines for immune-mediated myositis are indicated in Table 15.

**Table 15: Management guidelines for immune-mediated myositis**

Event	Management
Grade 1	<ul style="list-style-type: none"> <li>Continue atezolizumab</li> <li>Refer patient to rheumatologist or neurologist</li> <li>Initiate treatment as per institutional guidelines.</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset<sup>a</sup> and contact ETOP Medical Affairs.</li> <li>Refer patient to rheumatologist or neurologist.</li> <li>Initiate treatment as per institutional guidelines.</li> <li>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.</li> <li>If corticosteroids are initiated and event does not improve within 48 hours after initiation corticosteroids, consider adding an immunosuppressive agent.</li> <li>If event resolves to Grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>Withhold atezolizumab for up to 12 weeks after event onset<sup>a</sup> and contact ETOP Medical Affairs.</li> <li>Refer patient to rheumatologist or neurologist.</li> <li>Initiate treatment as per institutional guidelines.</li> <li>Respiratory support may be required in more severe cases.</li> <li>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.</li> <li>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>If event resolves to grade 1 or better, resume atezolizumab.<sup>b</sup></li> <li>If event does not resolve to grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>For recurrent events, treat as grade 4 event.</li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>Permanently discontinue atezolizumab and contact ETOP Medical Affairs.<sup>c</sup></li> <li>Refer patient to rheumatologist or neurologist.</li> <li>Initiate treatment as per institutional guidelines.</li> <li>Respiratory support may be required in more severe cases.</li> <li>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.</li> <li>If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>If event resolves to grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> </ul>

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  $\leq 10$  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  $\geq 1$  month to  $\leq 10$  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).

### 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)<sup>65</sup>. A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever  $\geq 38.5^{\circ}\text{C}$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin  $< 90$  g/L (9 g/dL) ( $< 100$  g/L [10 g/dL] for infants  $< 4$  weeks old)
  - Platelet count  $< 100 \times 10^9/\text{L}$  (100,000/ $\mu\text{L}$ )
  - ANC  $< 1.0 \times 10^9/\text{L}$  (1000/ $\mu\text{L}$ )
- 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  $\geq 2$  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)<sup>66</sup>. 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  $\leq 181 \times 10^9/\text{L}$  (181'000/ $\mu\text{L}$ )
  - AST  $\geq 48$  U/L
  - Triglycerides  $> 1.761$  mmol/L (156 mg/dL)
  - Fibrinogen  $\leq 3.6$  g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 16.

**Table 16: Management Guidelines for Suspected HLH or MAS**

Event	Management
Suspected HLH or MAS	<ul style="list-style-type: none"> <li>• Permanently discontinue atezolizumab and contact ETOP Medical Affairs (medical.affairs@ibcsg.org).</li> <li>• Consider patient referral to haematologist.</li> <li>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.</li> <li>• Consider initiation of IV corticosteroids and/or an immunosuppressive agent.</li> <li>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.</li> <li>• If event resolves to grade 1 or better, taper corticosteroids over <math>\geq 1</math> month.</li> </ul>

### 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 with known hypersensitivity to Chinese hamster ovary cell products or any component of the atezolizumab. Other medicinal products must not be co-administered through the same infusion line (see the latest version of the *Atezolizumab IB* for details).

## 14.2. Risks associated with bevacizumab

The most severe adverse events (AEs) identified in clinical studies with bevacizumab were GI perforations, haemorrhage (including tumour-associated haemorrhage and pulmonary haemorrhage/haemoptysis, which is more common in patients with NSCLC), and arterial thromboembolic events (ATE). Other AEs observed in patients treated with bevacizumab were fistulae, wound healing complications, hypertension, venous thromboembolism, and proteinuria. In addition, congestive heart failure was observed rarely and predominantly in patients with metastatic breast cancer who had received prior anthracycline-based therapy and prior chest wall radiation. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose-dependent.

The most frequently observed AEs across clinical studies in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea, and abdominal pain.

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 with chemotherapy alone.

There have been rare reports of patients treated with bevacizumab who developed signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES). Very rare cases of

hypertensive encephalopathy have also been reported, some of which were fatal (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 adverse reactions have been reported:

**Very common** ( $\geq 10\%$ ): 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, cough, hypomagnesaemia, hyponatraemia.

**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 erythrodysesthesia syndrome, fistula, muscular weakness, myalgia, back pain, pelvic pain, lethargy.

#### 14.2.2. Special warnings and precautions for use

##### 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. Bevacizumab 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 (TE) 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 GI 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. Bevacizumab 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, bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for 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.

### Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. 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 magnetic resonance imaging (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 grade 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 reactions.

### 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  $\leq 3$  need to be closely monitored.

## Haemorrhage

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be permanently discontinued 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 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.

## Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

## 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. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in the AVF3694g study who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline plus bevacizumab group compared to the treatment with anthracyclines only. CHF grade

3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment

### 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.

### 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.

### 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.](#)

### Severe eye infections following compounding for unapproved intravitreal use

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. [These reactions included infectious endophthalmitis, intraocular](#)

inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

#### Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

#### 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 leukopenia, 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  $\geq 3$  (despite optimal supportive care)

If toxicity resolves or reverts to CTCAE v5.0 grade  $\leq 1$  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@ibcs.org) as needed.

If toxicity does not resolve to CTCAE v5.0 grade  $\leq 1$  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 17).
- Proteinuria grade 3; resume bevacizumab once grade 2 (refer to Table 18 for details regarding dipstick and 24-hour urine collection) or less has been attained.
- Grade 3 or 4 bevacizumab-related events (except grade 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  $\geq 3$  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  $\geq 2$  fistula formation involving an internal organ
- Cerebral or cardiac ischemic events
- Grade  $\geq 3$  left ventricular dysfunction (CHF)
- Wound dehiscence and wound healing complications requiring medical intervention
- Nephrotic syndrome.
- CNS bleeding (any grade) or grade  $\geq 3$  bleeding of any kind
- Grade  $\geq 2$  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 17: 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 ( $\geq 24$ 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 $\geq 160$ mmHg or diastolic BP $\geq 100$ 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 18: Management of proteinuria**

	CTCAE description	Action
Grade 1	Urine protein level $\leq 1$ g/24 hrs (urine dipstick 1+)	No bevacizumab dose modification

	CTCAE description	Action
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  $\geq 3$ )
  - First occurrence: discontinue bevacizumab, until toxicity has improved to grade  $\leq 1$  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  $\geq 2$  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 (NCT01633970). 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 ( $\geq 20\%$ ) 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 (NCT01984242) 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 renal cell carcinoma (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).

IMotion151 (NCT02420821) is a Phase III, open-label, randomized study of atezolizumab (1200 mg i.v. Q3W) 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 untreated advanced RCC. The safety data presented is based on 897 patients; 451 patients in Arm A (atezolizumab plus bevacizumab); 446 patients in Arm B (sunitinib). The duration of exposure to study treatment for both atezolizumab (median: 12.0 months) and bevacizumab (median: 11.6 months) in the atezolizumab plus bevacizumab arm was longer than exposure for sunitinib (median: 9.2 months) in the sunitinib arm.

The overall safety experience in this study was consistent with the known safety profiles of each individual study drug and was consistent between the overall safety-evaluable population and the PD-L1-selected safety-evaluable population. No new safety signals were identified.

IMpower150 (NCT02366143) 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.<sup>50</sup>

## **14.4. Contraception, nursing, pregnancy**

### **14.4.1. Contraception**

Female patients who are not of childbearing potential due to being postmenopausal ( $\geq 2$  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 15.8.1. 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 15.8.

### 15.1. Adverse events

An adverse event (AE) is defined as any untoward medical occurrence that occurs from the date of randomisation 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 *Adverse Events eCRFs*. Please refer to Section 15.7.1 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 15.7.4) 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 15.7.16 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
- 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 v5.0; see Section 15.7.3); 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 *Adverse Events 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 Reports)**. See Section 15.8 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 15.7.16).
- 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* 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*. See Section 15.8 for detailed reporting instructions.

- 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  $> 3 \times \text{ULN}$  (or  $> 3 \times$  baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin  $> 2 \times \text{ULN}$  (of which  $\geq 35\%$  is direct bilirubin)
- Treatment-emergent ALT or AST  $> 3 \times \text{ULN}$  (or  $> 3 \times$  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  $> 10 \times \text{ULN}$
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and immune-mediated reactions
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade  $\geq 2$  cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune haemolytic anaemia
- Severe cutaneous **adverse** reactions (**SCARS**) (e.g. Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

## 15.6. Special Situations

Special Situations do not necessarily lead to an AE or SAE, but are required to be reported by the investigator to ETOP as such on the *SAE eCRFs* by indicating that this is a “Special Situation”.

The following Special Situations should be reported even in the absence of an AE/SAE:

Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors) and data related to breastfeeding.

### Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects

### Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the Marketing Authorization.

### Intercepted medication error

This refers to situations where a medication error occurred, and an intervention caused a break in the chain of events in the treatment process before reaching the patient. The intervention has prevented actual harm being caused to the patient.

### Medication Error

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (including potential medication errors or intercepted medication errors).

### Potential medication error

This refers to the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. It refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process.

### Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

### Breastfeeding

This refers to situation following exposure to a medicinal product from breast milk in infants

## 15.7. 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).

### 15.7.1. Adverse event reporting period

All AEs, regardless of relationship to the protocol treatment, will be reported from the date of randomisation 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*.

### 15.7.2. 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?"

### 15.7.3. Assessment of severity of adverse events

The adverse event severity grading scale for the CTCAE v5.0 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](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.

#### 15.7.4. 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 19: Relationship to the protocol treatment**

Not suspected	Suspected / related to protocol treatment
<ul style="list-style-type: none"> <li>- unrelated</li> <li>- unlikely</li> </ul>	<ul style="list-style-type: none"> <li>- possible</li> <li>- probable</li> <li>- definite</li> </ul>

#### 15.7.5. 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*.

#### 15.7.6. Infusion-related 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.

#### 15.7.7. 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.

#### 15.7.8. 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.

#### 15.7.9. 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 Reports 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*.

#### 15.7.10. 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*.

#### 15.7.11. 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).

#### 15.7.12. 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  $>3\times$  baseline value in combination with total bilirubin  $>2\times$  ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST  $>3\times$  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*.

#### 15.7.13. Deaths

For the ABC-lung protocol, mortality is a secondary 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 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 Reports)* 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 Reports)*. 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*.

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

#### 15.7.14. 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 *Screening 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").

#### 15.7.15. Lack of efficacy or worsening of the underlying disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 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.

#### 15.7.16. 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 not 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

### 15.8. Reporting of serious adverse events, adverse events of special interest and special situations

Any SAE, whether related to protocol treatment or not, or any AESI (see Section 15.5) and “Special Situations” (see Section 15.6) will be reported from the date randomisation 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 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 **SAE CRFs (SAE Reports)**

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

- Any SAE must be reported by submitting the completed *SAE eCRF (SAE Reports)* in English within 24 hours of awareness in the EDC system ETOPdata.
- Outcome must be reported on the *SAE eCRF*. If ongoing at the time of submission, the form must be updated once resolved. Your centre will receive reminders, at regular intervals, to update this form until the event has resolved.
- Queries may be issued by the ETOP safety office; a timely response by the investigator to all SAE-related queries is crucial.
- All SAEs that have not resolved upon discontinuation of the patient's participation in the trial must be followed until resolved, resolved with sequelae, not resolved (death due to another cause) or death (due to the SAE). If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be provided within 24 hours.

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 (SAE Reports)* 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

#### 15.8.1. 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**.

### 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**.

### 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 be asked 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.

### **15.9. 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
- Paclitaxel 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

This is a selection design, randomised trial with two non-comparative parallel arms.

Independently in each arm, the following hypothesis will be tested

- $H_0$ : 12-month PFS rate ( $\pi_0$ )  $\leq 0.18$ , versus
- $H_1$ : 12-month PFS rate ( $\pi_1$ )  $> 0.18$ , evaluated at  $\pi_1 = 0.37$ .

A sample size of 45 evaluable patients (per arm) will provide a power of 83%, for testing the above efficacy hypothesis, using an exact test for a single proportion, at the one-sided alpha of 0.025 (attained 0.023). Assuming 5% non-evaluable patients, the required total number of randomized patients for both arms increases to 95.

Sample size and power calculations for each arm separately have been performed using the EAST version 6.4 software.

Stratification based on prior use of third-generation EGFR TKI (e.g. osimertinib) or not.

The report from the primary analysis will be available approximately 2.5 years after the inclusion of the first patient (see Section 6).

## 17. Statistical analysis

### 17.1. Analysis populations

#### 17.1.1. ITT cohort

The Intention-to-treat (ITT) cohort of the trial includes all eligible patients randomised in the trial. Patients will be evaluated in the treatment arms to which they were randomly assigned, regardless of the treatment actually received, including randomised patients who did not receive any protocol treatment.

#### 17.1.2. Primary efficacy cohort

The primary efficacy cohort of the trial, that is the cohort based on which the primary hypotheses will be formally tested. It will include all patients randomised in the trial evaluable for the primary endpoint (12-month PFS). That is, the primary efficacy cohort will not take into account patients lost from follow-up before a PFS event or earlier than one-year of follow-up. Patients will be evaluated in the

treatment arms to which they were randomly assigned, regardless of the treatment actually received, including randomised patients who did not receive any protocol treatment.

### 17.1.3. 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 endpoint, 12-month PFS rate. For patients reaching 12 months after randomization without a PFS event, the first scheduled (54-week) or unscheduled tumour assessment after this timepoint, will be taken into account for the evaluation of the primary endpoint. **Primary efficacy** analysis will be performed separately in each treatment arm based on the **primary** efficacy cohort.

The exact binomial one-sample test will be used for the primary efficacy hypothesis testing, within each arm separately. The conclusion will be based on examining whether or not the observed number of progression-free patients crossed the corresponding boundary (14 or more patients among the 45 evaluable in each treatment arm should be progression-free in the 12-month timepoint in order to reject the null hypothesis  $H_0$ : 12-month PFS rate ( $\pi_0$ )  $\leq 0.18$ , versus the alternative hypothesis  $H_1$ : 12-month PFS rate ( $\pi_1$ )  $> 0.18$ , evaluated at  $\pi_1 = 0.37$ ). The rate of progression-free patients at 12 months (over the total number of patients evaluable at the 12-month time-point) will be accompanied by 2-side 95% exact binomial CI. In the frame of formal **testing** of 12-month PFS, loss from follow-up before a PFS event or earlier than one-year of follow-up will be considered as competing risks, and will not be included in the evaluable patients (**primary efficacy cohort**).

**Further PFS analysis for each treatment arm will be based on the ITT cohort. Kaplan-Meier plots for PFS will be produced by arm, median PFS times and 12-month PFS rate with corresponding 95% CIs will be also estimated.** In addition, multivariable Cox proportional hazards models (stratified according to the stratification factor of previous use of third-generation TKI, e.g. osimertinib) will be also developed. Cox models will be adjusted for a series of variables of clinic pathological interest, and backward elimination (with removal criterion  $p > 10\%$ ) will be used for the selection of significant variables to be retained in the models.

As previously mentioned, the trial is not designed or powered to test for statistically significant differences in the PFS between the two treatment arms. A simple selection between the two arms could be conducted based on the numerical comparison in efficacy (12-month PFS rate) along in comparison

with toxicity, leading to the selection of the more promising treatment (but this will not be a statistical superiority finding).

Statistical analysis for the primary as well as secondary endpoints will be described in detail in the Statistical Analysis Plan (SAP) document.

#### 17.2.2. Secondary efficacy analysis

Clinical efficacy (including intracranial/extracranial PFS, OS and ORR) will be further assessed separately for the two treatment arms, stratified by the randomisation stratification factor. The secondary efficacy analysis will be based on the ITT cohort.

OS, along with median OS and 12-month OS rate will be estimated, and graphically illustrated, by arm, based on the Kaplan-Meier approach, while Cox models will be also developed (in an analogous manner as those for the primary PFS).

Analogous will be the analysis of intracranial and extracranial PFS. Furthermore, since death and extracranial progression are competing risks to intracranial PFS, univariable and multivariable Fine-Grey competing risk regression will be used to compare the cumulative incidence rate of intracranial recurrence rate.

Cumulative incidence plots of CNS progression, non-CNS progression, and death, will be also presented by arm.

ORR along with corresponding 95% exact-binomial CIs will be presented by treatment arm.

Logistic regression models of the “response” or “disease control” status will be further applied, adjusting for the stratification factor and variables of clinical interest.

### 17.3. 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 (AEs overall, by grade, all-cause AEs, treatment-related AEs, serious AEs etc.) will be presented in tabular and graphical format by treatment arm. Selected lab parameters and vital signs will be analysed by treatment arm.

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.

## 17.4. Other exploratory analyses

### 17.4.1. Quality of life

Changes in EORTC QLQ-30 and LC13 functional, symptom and global scales from baseline will be analysed descriptively (median, min, max). The minimally important difference (MID) is defined as the smallest change in a QoL score considered important to patients. For the interpretation of MIDs for the EORTC-QLQ-30 scales we will rely on published guidelines.<sup>67,68</sup>

TTD is defined as the time from baseline to the first time the patient's score shows a  $\geq 10$ -point increase/decrease (higher scores for symptoms indicate worse, higher scores for function scale indicate better condition) above baseline in the EORTC-QLQ-C30 global health/ QoL scale and LC13 symptoms /subscales (cough, dyspnoea, and chest pain). The primary outcome will be the global health/ QoL scale. In order for a scale/symptom to be considered "deteriorated," a score increase of  $\geq 10$  points above baseline must be held for at least two consecutive assessments or an initial score increase of  $\geq 10$  points is followed by death within 3 weeks from the last assessment.

TTD endpoint will be analysed as a time-to-event endpoint. Kaplan-Meier plots and estimates by treatment arm will be produced, arms will be compared based on stratified log-rank test, and corresponding HRs with 95% CIs will be produced.

Reasons for missing data will be assessed for each scheduled assessment with no available QoL data and presented in frequency tables. 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.

Longitudinal models will be also used to test changes over time in the EORTC-QLQ-C30 and LC13 subscales/symptoms. Models will be adjusted for patient and disease characteristics (including age, sex, smoking status, ECOG performance status, TNM staging) and account for missing responses.

### 17.4.2. Summaries of treatment group comparability

Patient as well as tumour baseline characteristics (including age, sex, smoking status, ECOG performance status, TNM staging and medical history) will be summarised by treatment arm. Variables in categorical scale will be presented with proportions, while variables in continuous scale will be analysed using means, standard deviations, medians, and ranges. Summaries will be presented by treatment group as well as overall. Differences between treatment groups will be statistically assessed based on Fisher's exact test (for categorical variables) and Mann-Whitney test (for continuous variables), with 5% level of significance.

### 17.4.3. Further exploratory analyses

Further exploratory analyses include descriptive subgroup analyses of primary and secondary efficacy measures, by treatment arm, according to the following:

- prior use of third-generation EGFR TKI (e.g. osimertinib) or not
- EGFR mutation subtype (del19 versus L858R)
- PD-L1 expression levels (<1%, 1-49%, ≥50% of PD-L1 expression in tumour tissue). Additional cut-offs could be considered in a further secondary exploratory.

Results will be graphically illustrated through the use of forest-plots.

Additional, analogous exploratory analyses will be performed, based on the availability of translational data (e.g. tumour mutational burden).

## DATA COLLECTION AND MANAGEMENT

### 18. Quality of Life Assessment

#### 18.1. Quality of Life Measure

Quality of life will be assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the lung cancer-specific module (QLQ-LC13). The QLQ-C30 is a 30-item self-report questionnaire with a one-week recall period. It is composed of multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive functioning), three symptom scales (fatigue, nausea/vomiting and pain) and a global scale combining the two items assessing global health status and global QoL. Single items include dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties.<sup>47</sup> The QLQ-LC13 measures lung cancer associated symptoms (cough, haemoptysis, dyspnoea, and site-specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia).<sup>48</sup> EORTC scoring guidelines will be used to calculate scores.

#### 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 12 months. The paper-based QoL questionnaire is to be completed by the patient during the visits at the hospital, i.e.: at screening, [within 3 days before treatment administration](#) in cycles 2-7 (i.e., at weeks 3, 6, 9, 12, 15, and 18) and every 6 weeks thereafter OR

until disease progression OR a maximum of 12 months, 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 *ABC-lung 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 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 20: Case report form schedule**

eCRF in ETOPdata	To be completed
EL - Eligibility Check and Randomisation	Within 42 calendar days of written informed consent signature
S - Screening	Within 14 calendar days after randomisation
TA - Tumour Assessments	<u>Baseline before randomisation:</u> within 14 calendar days after randomisation; <u>After randomisation:</u> within 14 calendar days of date of each radiological imaging.
TV –Treatment Visit	Within 14 calendar days after each treatment visit.

eCRF in ETOPdata	To be completed
AE - Adverse Events	Continuously from randomisation to 90 calendar days after last dose of protocol treatment;  - Within 14 calendar days of awareness of AE.
CM – Concomitant Medications	Continuously within 14 days prior to 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.
SAE - SAE Reports	Within 24h of awareness of SAE (from date of randomisation to 90 calendar days after the last dose of protocol treatment), <a href="#">AESI</a> or “Special Situations”.  All SAEs, AESIs and “Special Situations” must be submitted via ETOPdata, submission via fax to ETOP safety office only in case of unavailability of ETOPdata
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	<u>Maternal exposure:</u>  Within 24h after awareness of pregnancy;  Within 14 calendar days of end of pregnancy.  <u>Paternal exposure (pregnancy in a female partner of a male trial participant):</u>  Within 24 hours after awareness of pregnancy outcome.
QoL - Quality of Life	<a href="#">Baseline before randomisation:</a>  <a href="#">within 14 calendar days after randomisation;</a>  <a href="#">After randomisation:</a>  within 28 calendar days after completion of questionnaire.

eCRF in ETOPdata	To be completed
BMT - Biological Material Tracking	<p>This eCRF is to be completed incrementally.</p> <p>Entries are to be made:</p> <ul style="list-style-type: none"> <li>- Within 4 weeks after randomisation: for information pertaining to “FFPE Tumour tissue: at baseline” (prior to randomisation);</li> <li>- Immediately after local storage of blood samples (on same day): for information pertaining to “Blood samples at baseline”, “Blood samples at Day 1 of Cycle 3” and “Blood samples at Progression”;</li> <li>- Within 14 calendar days of progression: for information pertaining to “FFPE Tumour tissue at progression” (after protocol treatment, strongly recommended);</li> <li>- Immediately (on same day) after submission of material (FFPE) for central biobanking: for field “Date Specimen sent to Central Lab”.</li> </ul>
WC/LFU – Withdrawal of Consent / Lost to Follow-Up	Within 14 calendar days of awareness of withdrawal of consent or loss to follow-up.

## 19.2. Documents to be uploaded on ETOPdata

- Copy of pathology report (including the results from EGFR mutation testing)
- Copy of quality of life form

## 19.3. Queries Resolution Schedules

**Table 21: 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 15 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 19.3). 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, AE documentation, dispensing protocol treatment, compliance with protocol, drug accountability, concomitant therapy use, quality of data and storage of blood and serum samples.

#### **23.3. Quality assurance**

ETOP conducts periodic 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**

### **24. 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).

#### **24.1. 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.

## **24.2. 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.

## **25. 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 legal representative in accordance with the law of the country in which the trial is to take place.

If a patient is unable to read and write, he/she may give verbal consent to participate in the trial. In this situation, a witness must sign the informed consent form on his/her behalf.

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.

## **26. Confidentiality and data protection**

ETOP maintains confidentiality standards by coding all patients enrolled 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

## 27. Governance

### 27.1. 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.

### 27.2. 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 interim clinical outcome. 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 15-19 ABC-lung 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.

### 27.3. 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.

## 28. Administrative issue

### 28.1. Final report

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

### 28.2. Publication

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

### **28.3. 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.

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