Official Title: A Phase III, Randomized, Double Blind, Placebo-Controlled, Multicentre Study of The Efficacy And Safety of Atezolizumab Plus Chemotherapy for Patients with Early Relapsing Recurrent (Inoperable Locally Advanced or Metastatic) Triple-Negative Breast Cancer

NCT Number: NCT03371017

Document Date: Protocol Version 9: 25-Jan-2023

PROTOCOL

TITLE:	**A PHASE III, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS CHEMOTHERAPY FOR PATIENTS WITH EARLY RELAPSING RECURRENT (INOPERABLE LOCALLY ADVANCED OR METASTATIC) TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	MO39193
VERSION NUMBER:	9.0
TEST PRODUCT:	Atezolizumab (RO5541267, MPDL3280A)
REGULATORY AGENCY IDENTIFIER NUMBERS	*EUDRACT Number*: *2016-005119-42* *IND Number*: *123,277*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic *signature and* date stamp *on the final page of this document.*

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
9	See electronic date stamp on the final page of this document
8	12 November 2021
7	13 January 2021
6	18 December 2020
5	26 February 2020
4	26 August 2019
3	18 February 2019
2	10 November 2017
1	16 August 2017

PROTOCOL AMENDMENT, VERSION 9.0: RATIONALE

Protocol MO39193 (IMpassion132) has been amended to include updates following the Atezolizumab Investigator Brochure Version 19 release. Changes to the protocol, along with rationale for each change, are summarized below:

- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19 and Addendum 1 to the Atezolizumab Investigator's Brochure, Version 19 (Appendix 10).
- The adverse event management guidelines have been updated to align with the Addendum 2 to the Atezolizumab Investigator's Brochure, Version 19 (Appendix 10).
- Additional details on timing of analysis of China population have been provided to align with Statistical Analysis Plan (SAP) (Sections 3.2.1, 6.1.1).
- The current indication-specific companion diagnostics approval status of the VENTANA programmed death ligand 1 (PD-L1) (SP142) Assay for the assessment of the PD-L1 protein has been updated (Section 3.3.5).
- Due to potentially still ongoing enrolment of patients in China at the time of primary endpoint analysis, clarification has been added to indicate that treatment unblinding at the study level at the time of primary endpoint analysis will only apply to randomized patients. Unblinding at the study level does not apply to patients who have not been randomized at the time of primary endpoint analysis (Section 4.2.3.3).
- Clarification has been added to indicate that if local triple negative breast cancer (TNBC) testing is chosen for determination of eligibility, prospective central testing for eligibility purposes should not be requested. Retrospective testing for central confirmation of TNBC will be performed but will have no impact on eligibility (Sections 4.5.6.1 and 4.5.6.2.4).
- Text has been added to indicate that the VENTANA PD-L1 (SP142) CDx Assay is investigational (Section 4.5.6.2.3).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.9.6).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Section 5.1.2).
- The list of risks associated with atezolizumab and the list of adverse events of special interest has been revised to include myelitis and facial paresis (Sections 5.1.2, 5.2.3).
- The list of identified risks for atezolizumab has been revised to include pericardial disorders (Section 5.1.2).
- The reference to reporting associated signs and symptoms of an infusion related reaction (IRR) on the dedicated Infusion-Related Reaction eCRF has been removed, since there is no separate eCRF page to record these. Signs and symptoms should be reported in the "Additional Case Details" field of the Adverse Event page (Section 5.3.5.1).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.

- Patient-Reported Outcomes (PRO) evaluable population has been removed, as PRO analysis will be done using PD-L1 (SP142) positive population and the modified intent to treat (mITT) population (Sections 6.4.2, 6.4.2.6).
- Analysis on Functional Assessment of Cancer Therapy – General (FACT-G) has been revised to align with SAP. In particular, descriptive analysis of the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported using the PD-L1 (SP142)-positive population and the mITT population. Additionally, the proportion of patients reporting improvement, deterioration or no change in symptoms following the first assessment will be provided (Section 6.4.3.2).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Clinical Trial Regulation (CTR) requirements (Section 8.4).
- The number of participation study sites has been updated from 100 to 135 to reflect the current number of participating study sites (Section 9.5).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- Appendix 5 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti cancer agent.
- Appendix 5 has been revised to include autoimmune myelitis.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS CHEMOTHERAPY FOR PATIENTS WITH EARLY RELAPSING RECURRENT (INOPERABLE LOCALLY ADVANCED OR METASTATIC) TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	MO39193
VERSION NUMBER:	9.0
EUDRACT NUMBER:	2016-005119-42
IND NUMBER:	123277
TEST PRODUCT:	Atezolizumab (RO5541267, MPDL3280A)
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS CHEMOTHERAPY FOR PATIENTS WITH EARLY RELAPSING RECURRENT (INOPERABLE LOCALLY ADVANCED OR METASTATIC) TRIPLE-NEGATIVE BREAST CANCER**
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EUDRACT NUMBER:	2016-005119-42
IND NUMBER:	123277
TEST PRODUCT:	Atezolizumab (RO5541267, MPDL3280A)
PHASE:	Phase III
INDICATION:	Triple-negative breast cancer (TNBC)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with inoperable *locally advanced or metastatic* triple-negative breast cancer (TNBC). Eligible patients should have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. Patients must have experienced disease progression within 12 months (<12 months) from the last treatment with curative intent for early breast cancer (eBC). Specific objectives and corresponding endpoints for the study are outlined in **Table 1** below.

Table 1 Study Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy.	• Overall survival (OS), defined as time from randomisation to death from any cause. OS will be tested hierarchically in the following fixed order: o In the population with programmed death-ligand 1 (PD-L1)-positive tumour status, as defined in Section 6; o In the modified intent-to-treat (mITT) population, as defined in Section 6.

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy.	• 12-month survival rate, defined as the proportion of patients alive 12 months after randomisation. • 18-month survival rate, defined as the proportion of patients alive 18 months after randomisation. • Progression-free survival (PFS), defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or death from any cause, whichever occurs first. PFS will be tested hierarchically in the following fixed order: o In the PD-L1-positive population, as defined in Section 6; o In the mITT population, as defined in Section 6. • Objective response rate (ORR), defined as the proportion of patients with an objective response, defined as a complete response (CR) or a partial response (PR), as determined by the investigator according to RECIST 1.1. ORR will be tested hierarchically in the following fixed order: o In the PD-L1-positive population, as defined in Section 6; o In the mITT population, as defined in Section 6. • Duration of objective response (DoR), defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST 1.1, or to death from any cause, whichever occurs first. • Clinical benefit rate (CBR), defined as the proportion of patients with a CR or a PR or stable disease (SD) that lasts ≥ 6 months, as determined by the investigator according to RECIST 1.1. In addition, confirmed objective response rate (C-ORR) and duration of confirmed response (C-DoR) will be analysed. Details will be provided in the Statistical Analysis Plan (SAP).
• To evaluate patient-reported outcomes (PROs) of global health status (GHS)/quality of life (QoL) associated with atezolizumab plus chemotherapy compared with chemotherapy alone, as measured by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).	• Time to confirmed deterioration (TTD) of GHS/QoL, defined by a minimally important decrease of ≥10 points at two consecutive assessment time-points on the GHS/QoL scale (Items 29, 30) of the EORTC QLQ-C30.

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives:	
• To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab plus chemotherapy compared with placebo plus chemotherapy, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23).	• Mean and mean changes from baseline in function (role physical, emotional, social, cognitive) and disease/treatment-related symptoms by treatment cycle, as assessed by the function scales and all symptom items/scales of the EORTC QLQ-C30 and the QLQ-BR23.
• To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to chemotherapy compared with placebo plus chemotherapy, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical wellbeing subscale of the Functional Assessment of Cancer Therapy: General (FACT-G) quality of life instrument.	• Proportion of patients reporting each response option at each assessment time point for item GP5 from the FACT-G.
• To evaluate health utility as measured by the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire, to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L questionnaire
Specific Efficacy Objectives for Patients Recruited in China:	
• The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus chemotherapy compared with placebo plus chemotherapy as measured by OS and other efficacy endpoints in the China population (enrolled in the Global study and during additional recruitment in China) is consistent with the efficacy observed in the Global population (Global study).	• As described for the Global study.

Objectives	Corresponding Endpoints
Safety Objectives:	
• To evaluate the safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy.	• Incidence, nature, and severity of adverse events (AEs), with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE 4.0). • Change from baseline in targeted vital signs and physical findings. • Change from baseline in targeted clinical laboratory test results.
Pharmacokinetics Objectives:	
• To characterize the pharmacokinetics (PK) of atezolizumab when administered with carboplatin/gemcitabine or with capecitabine in patients with breast cancer.	• Peak and trough of atezolizumab concentrations in serum (Cmax and Cmin) at specified time points during treatment.
Immunogenicity Objective:	
• To evaluate the immunogenicity of atezolizumab.	• Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline.
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs.	• Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objectives:	
• To assess the efficacy and safety of atezolizumab plus chemotherapy according to programmed death−ligand 1 (PD-L1) status.	• Relationship between PD-L1 protein expression by immunohistochemistry (*VENTANA PD-L1 (SP142) Assay*) in screening tumour tissue and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC1/2/3).

Objectives	Corresponding Endpoints
Exploratory Biomarker Objectives:	
• To assess biomarkers that are predictive of response to atezolizumab (i.e., predictive biomarkers), are associated with outcomes independent of treatment (i.e., prognostic biomarkers), as well as pharmacodynamic exploratory biomarkers in tumour tissue (e.g., screening, on-treatment*, and at disease progression sample*) and blood* and their association with disease status and/or response to study drug. • To assess changes in blood-* and tissue-based biomarkers during chemotherapy +/- atezolizumab treatment. • To assess whether immune biomarker findings from this study are consistent with findings in other studies in TNBC or in other tumour types.	• Relationship between tumour immune-related or disease type-related biomarkers (including but not limited to TILs and cluster of differentiation CD8) by immunohistochemistry in tumour tissues, and clinical outcomes. • Relationship between PD-L1 status measured by various immunohistochemistry assays and clinical outcomes. • Relationship between certain molecular subgroups and pre-defined gene signatures by ribonucleic acid (RNA) expression analysis in tumour tissues, and clinical outcomes. • Relationship between deoxyribonucleic acid (DNA) mutations and mutational burden assessed in tumour tissues, and clinical outcomes. • Relationship between exploratory biomarkers (including but not limited to circulating cell-free DNA, proteins and cytokines) in plasma* collected before treatment, during treatment and at disease progression, and clinical outcomes. • Changes in blood-* and tissue- based biomarkers under chemotherapy +/- atezolizumab treatment in relation to clinical outcome. • Correlation of immune biomarker findings in blood* and tissue samples from this study to findings from other studies in TNBC and other tumour types.

* Plasma, whole blood, and optional tumour samples (on-treatment and at disease progressions) for exploratory biomarker analyses will not be collected from patients enrolled in mainland China. Patients enrolled in mainland China will only contribute to exploratory biomarker analyses based on mandatory tumour tissue samples collected at screening. The number of required slides for exploratory analyses using tumor tissue samples are contingent upon the review and approval of the exploratory research by each site's Institutional Review Board/Ethics Committee (IRB/EC), and upon the review and approval by the Human Genetics Resources Administration of China (HGRAC) exploratory application.

All requirements described in this protocol apply to the Global Study, unless otherwise specified; requirements specific to the China population are marked as such throughout the protocol.

Study Design

Description of Study

This is a phase III, global, double-blind, two-arm, placebo-controlled, randomised study designed to evaluate the efficacy and safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with inoperable *locally advanced or metastatic* TNBC. Eligible patients should have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. Patients must have experienced disease progression within 12 months (<12 months) from the last treatment with curative intent for eBC.

Global Study: A total of approximately 572 patients will be randomised in the study. Following the enrolment of 382 patients with inoperable *locally advanced or metastatic* TNBC (irrespective of programmed death-ligand 1 [PD-L1] tumour status, referred to as 'all-comers'), approximately 190 additional patients with PD-L1-positive tumour status will be randomised, in order to reach

approximately 330 patients with PD-L1-positive tumour status required for the primary endpoint analysis of overall survival (OS) in the PD-L1 positive population.

Additional Enrolment in China: After approximately 572 patients have been randomised in the Global study, global recruitment will be closed. Additional patients with PD-L1-positive tumour status may be subsequently randomised in China only, following the same randomisation procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1-positive tumour status in mainland China (including patients from China enrolled in the Global study), referred to as the China population. The schedule of assessments and study treatments for these patients will be identical to those in the Global study, with the following exceptions: patients enrolled in mainland China will not undergo plasma, whole blood, and optional tumour sample collections for exploratory biomarker assessments. Analyses based on the China population will be performed and summarised separately.

The following applies to all patients randomised in the study unless otherwise noted.

Patients who do not meet the criteria for participation in this study (screen failure), may qualify for an additional re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion.

Patients are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log. See Section 4.5.1.

Results of screening tests within the protocol-defined screening window may be used rather than repeating required tests. For patients who are re-screened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria.

Patients will be assessed for eligibility during the 28-day screening period prior to enrolment and randomisation; refer to Appendix 1 for details. A screening tumour sample must be tested at the designated central study laboratory to assess PD-L1 expression and either locally or at the designated central study laboratory to confirm triple-negative tumour status before a patient will be considered eligible for the study. TNBC is defined as human epidermal growth factor 2 (HER2), oestrogen receptor (ER) and progesterone receptor (PR) negative disease determined in accordance with the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (HER2: Wolff et al. 2018; ER and PR: Hammond et al. 2010; Allison et al. 2020). Triple-negative tumour status assessed locally prior to randomisation requires subsequent confirmation (retrospectively) by the designated central laboratory.

A representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen will be tested for PD-L1 expression, as assessed by central laboratory using the *investigational VENTANA PD-L1 (SP142) Assay*. Tumor tissue should be of good quality based on total and viable tumor content and must be prospectively evaluated for PD-L1 expression prior to randomisation. A tumor specimen obtained from relapsed metastatic or locally advanced disease may be submitted, if clinically feasible. If a fresh tumour sample is not clinically feasible, either the primary diagnosis, the surgical resection sample, or the most recent formalin-fixed, paraffin-embedded (FFPE) tumour biopsy should be used.

Eligible patients will be randomised in a 1:1 ratio to receive atezolizumab with chemotherapy (**Arm A**) or placebo with chemotherapy (**Arm B**). For each patient, chemotherapy (carboplatin/gemcitabine or capecitabine) will be selected by the investigator prior to randomisation; however, capecitabine will be mandatory for patients who have received prior platinum therapy for the treatment of their eBC. Overall, and per country/region, approximately 30% of patients randomised in the study should receive capecitabine, and approximately 70% of patients should receive carboplatin/gemcitabine. Randomisation will be stratified by the following three factors: presence of visceral (lung and/or liver) metastases (yes vs. no), tumour PD-L1 status (tumour-infiltrating immune cell [IC] 0 vs. IC1/2/3) and chemotherapy choice (carboplatin/gemcitabine vs. capecitabine). Additional PD-L1 positive patients enrolled under protocol version 4.0 (and beyond) will only be stratified according to the presence of visceral metastases and chemotherapy choice.

Patients should receive their first dose of study treatment no later than 3 calendar days after randomisation. Study treatment will be delivered as follows:

Arm A

Atezolizumab 1200 mg by IV infusion on day 1 of each 3-week treatment cycle with either:

- gemcitabine 1000 mg/m^2, followed by carboplatin target area under the curve (AUC) 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle

  or

- capecitabine 1000 mg/m^2 twice daily orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle

Arm B

Placebo 1200 mg by IV infusion on day 1 of each 3-week treatment cycle with either:

- gemcitabine 1000 mg/m^2, followed by carboplatin target AUC 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle

  or

- capecitabine 1000 mg/m^2 twice daily orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle.

Study treatment will continue until disease progression per RECIST 1.1, unacceptable toxicity, or patient or investigator decision to discontinue treatment. Atezolizumab/placebo and chemotherapies may be discontinued for toxicity independently of each other in the absence of disease progression. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Patients who have been randomised will not be replaced.

Tumour assessments will be performed every 8 weeks (± 1 week) for the first 12 months after treatment initiation and every 12 weeks (± 1 week) thereafter until disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Tumour assessments will be performed according to the specified schedule regardless of dose delays, interruptions, or discontinuations. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumour assessments according to the protocol-specified schedule until they experience disease progression, withdraw consent, or die, or until the study closes, whichever occurs first, even if they started another anti-cancer therapy after study treatment discontinuation.

For estimation of PFS, ORR, and DoR, tumour response will be based on RECIST v1.1. Imaging data used for tumour assessment may be retrospectively collected by the Sponsor to enable centralised, independent review of response endpoints by an Independent Review Committee in the future, if necessary.

Cross-over between treatment arms will not be allowed.

Given that the primary efficacy endpoint of the study is overall survival (OS), every effort should be made to avoid unblinding. Treatment codes should not be broken except in emergency situations or in case of disease progression where knowledge of study treatment assignment will affect later-line treatment of the patient, as defined below. Upon radiographic disease progression per RECIST v1.1, and the resulting discontinuation of study treatment, the study drug assignment may be unblinded (for the patient with confirmed disease progression only), provided that the following conditions are met:

- There is an imminent plan to treat the patient with next line of approved treatment or enrolling her/him in a subsequent clinical trial; and
- There is documented evidence provided to the Sponsor that the patient meets the criteria for the next-line of approved treatment or clinical trial, except for invasive/radiation-requiring procedures; and
- The knowledge of treatment allocation (atezolizumab/placebo) in the current study is required to confirm that the patient meets the criteria for the next-line approved treatment or clinical trial; and
- Data entry related to the documented progression is entered in the eCRF; and
- The Investigator obtains Sponsor approval for the potential unblinding.

Survival data and post-study treatment cancer treatment information must continue to be collected for unblinded patients.

Safety assessments will include regular evaluation of AEs and conduct of physical examinations, vital signs, clinical laboratory tests (haematology, blood chemistry, urinalysis) and electrocardiograms (ECGs). AEs will be graded according to the NCI CTCAE v4.0.

PK and atezolizumab immunogenicity analyses will be based on blood samples collected before, during and after study treatment. A detailed schedule of sample collections for PK and immunogenicity analyses is included in Appendix 2.

Blood and tumour samples will be collected in order to conduct exploratory biomarker assessments investigating mechanisms of study treatment activity within the tumour microenvironment, possible resistance mechanisms, and potential predictive and prognostic indicators.

As described above, all patients enrolled in the Global study and all patients in the China population will undergo mandatory tumour sample collection at screening. The mandatory tumour sample submitted prior to enrolment for ER/PR, HER2 and PD-L1 testing will be included in the exploratory biomarker evaluations. The schedule of sample collections for biomarker research is included in Appendix 2. Acceptable tumour samples for biomarker analyses are core needle biopsies for deep tumour tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine needle aspirates, brushings, cell pellets from pleural effusions, samples from bone metastases, and lavage samples are not acceptable.

In addition, for patients enrolled in the Global study (except for patients enrolled in mainland China):

- Plasma samples will be collected at baseline, during treatment and at disease progression.
- A whole blood sample will be collected at baseline for germline mutation analyses.
- If deemed clinically feasible by the investigator, optional tumour samples for biomarker analyses will be collected pre-treatment on Day 1, Cycle 2 and at disease progression, provided that the patient consented to this optional procedure.

  Plasma, whole blood, and optional tumour samples for biomarker analyses will not be collected from patients enrolled in mainland China.

The schedule of sample collections for biomarker research is included in Appendix 2.

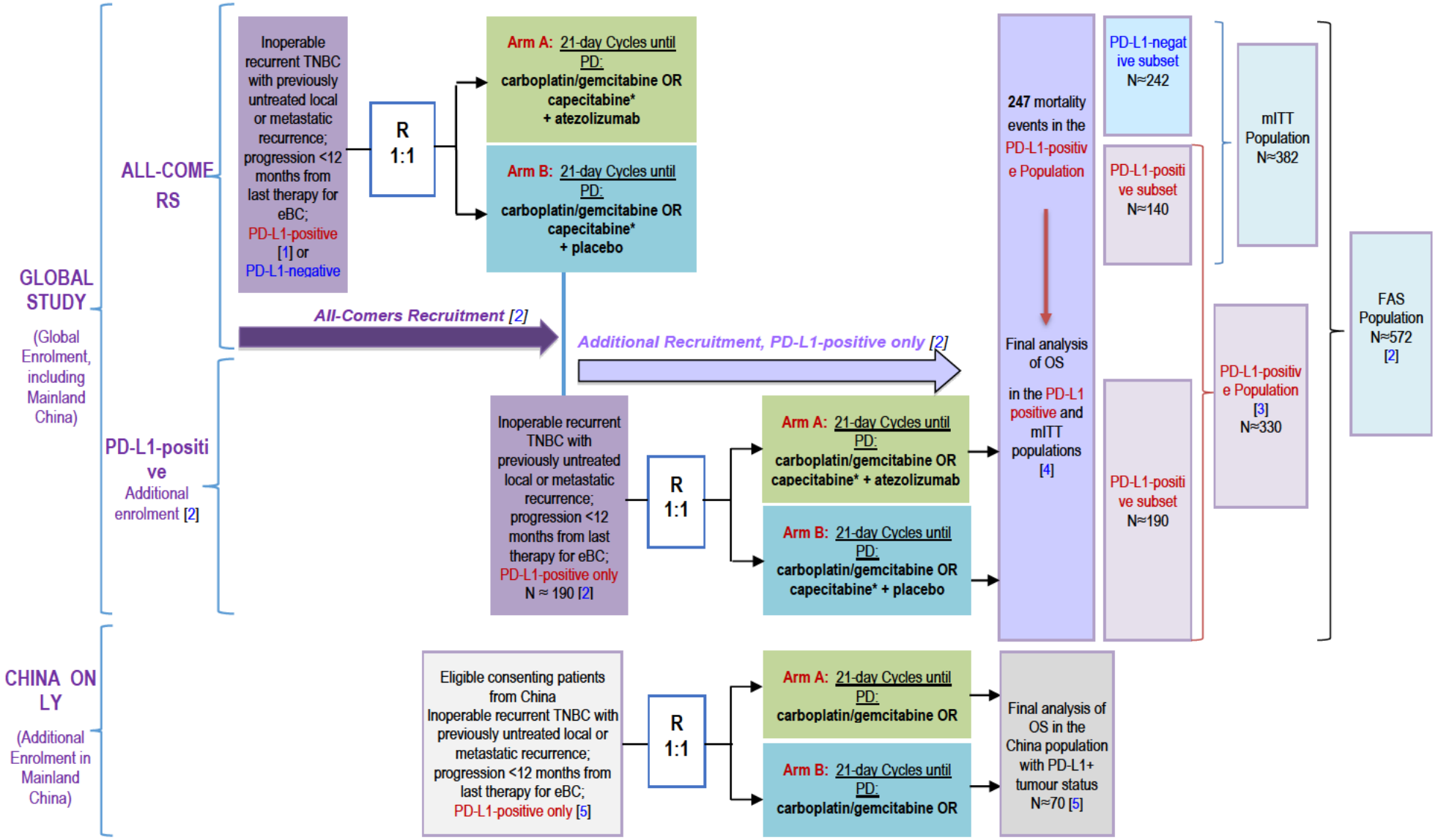
Patients will undergo a treatment discontinuation visit 30 days after their last study treatment and will immediately enter post-treatment follow-up. Patients will be followed for disease progression (if progression has not yet occurred) and survival every 3 months for at least 18 months from randomisation unless death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor occurs sooner. Anti-cancer treatments received during this follow-up period will be documented.

A Steering Committee (SC) will provide scientific oversight of the trial. Details of the composition and mandate of the SC will be provided in the SC Charter. In addition, an independent Data Monitoring

Committee (iDMC) will be in place for periodic review of aggregate safety data during the study and an interim efficacy analysis, should the latter occur. Details of the composition of the iDMC, the safety review plan and procedures for interim analyses will be provided in the iDMC Charter.

A schedule of activities is provided in Appendix 1. A study design schema is presented in **Figure 1** below.

Figure 1 Study Schema



D=day; FAS=Full Analysis Set; IV=intravenous; mITT=modified Intent-to-Treat (population); PD=disease progression; R=randomisation; PD-L1=programmed death-ligand 1; RECIST=Response Evaluation Criteria in Solid Tumors; TNBC=triple-negative breast cancer

[1] Based on 382 'all-comers' enrolled in the Global study, approximately 37% (N=140) of 'all-comer' patients have PD-L1-positive tumour status.

[2] Following the enrolment of 382 'all-comers', approximately 190 additional patients with PD-L1-positive tumour status will be randomised in a 1:1 ratio to receive atezolizumab with chemotherapy (Arm A) or placebo with chemotherapy (Arm B), for a total of approximately 572 patients randomised into the Global study (FAS).

[3] The PD-L1-positive population (defined as all patients randomised in the study whose PD-L1 status was IC1/2/3 at the time of randomisation) is the primary analysis population.

[4] No analysis is planned before the target number of OS events (247) is reached in the PD-L1-positive population. OS in the mITT population will also be analysed at that time.

[5] After approximately 572 patients have been randomised in the Global study (including patients from mainland China), global recruitment will be closed. Additional patients with PD-L1-positive tumour status may be subsequently randomised in China only, following the same randomisation procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1-positive tumour status in mainland China (including patients enrolled in the Global study), referred to as the China population.

Number of Patients

Global Study: The total Global study population will include approximately 572 randomised patients.

Following the enrolment of 382 all-comer patients, of which approximately 37% (140 patients) were found to have PD-L1-positive tumour status, approximately 190 additional patients with PD-L1-positive tumour status will be randomised, for a total of approximately 330 randomised patients with PD-L1-positive tumour status.

The study will be conducted at approximately *135* sites globally.

Additional Enrolment in China: As described above, after approximately 572 patients have been randomised in the Global study, global recruitment will be closed. Additional patients with PD-L1-positive tumour status may be subsequently randomised in China only, following the same randomisation procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1-positive tumour status in mainland China (including patients from China enrolled in the Global study).

Target Population

Inclusion Criteria

Patients must meet all the following criteria for study entry:

1. Have provided written informed consent
2. Male or female ≥ 18 years of age
3. In the investigator's judgment is willing and able to comply with the study protocol including completion of patient-reported outcomes questionnaires
4. Histologically confirmed TNBC that is either locally recurrent inoperable and cannot be treated with curative intent or is metastatic

   Triple-negative breast cancer, defined as the absence of HER2 overexpression, ER expression and PR expression, must be determined by either local or central testing of a screening tumour sample as defined by ASCO/CAP guidelines (HER2: Wolff et al. 2018; ER and PR: Hammond et al. 2010; Allison et al. 2020). See sample related inclusion criterion below.
5. Prior treatment (of early breast cancer) with an anthracycline and taxane
6. Documented disease progression (e.g., with biopsy sample, pathology, or imaging report) occurring within 12 months (<12 months) from the last treatment with curative intent, i.e.
   - date of the last chemotherapy administration, that included a taxane and anthracycline (neoadjuvant or adjuvant) or
   - date of the primary breast tumour surgery after neoadjuvant treatment

   whichever occurred last. Adjuvant radiation therapy must not be considered treatment with curative intent for purpose of calculating <12 months interval requirement.
7. Have not received prior chemotherapy or targeted systemic therapy for their locally advanced inoperable or metastatic recurrence

   Prior radiation therapy for recurrent disease is permitted. There is no required minimum washout period for radiation therapy; however, patients should have recovered from the effects of radiation before randomisation. Candidate lesions for palliative radiotherapy must be decided prior to study entry.

   China population only: Chinese traditional medicines with an approved indication for cancer treatment are permitted as long as the last administration occurred at least 2 weeks prior to randomisation.

8. Measurable or non-measurable disease, as defined by RECIST 1.1 (Note: previously irradiated lesions may be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation).
9. Availability of a representative formalin-fixed paraffin-embedded (FFPE) tumour block (preferred) or at least 17 unstained slides obtained from relapsed metastatic or locally advanced diseases may be submitted, if clinically feasible, with an associated pathology report, if available. If a fresh tumour sample is not clinically feasible, either the diagnosis sample, the primary surgical resection sample, or the most recent FFPE tumour biopsy sample should be used.
    a. The tumour tissue should be of good quality based on total and viable tumour content and must be evaluated centrally for PD-L1 expression, as determined using *investigational VENTANA PD-L1 (SP142) Assay* prior to enrolment, with positivity defined as ≥1% of the tumor area occupied by PD-L1- expressing tumor-infiltrating immune cells of any intensity, and either locally or centrally for HER2, ER, and PR expression prior to enrolment. Patients whose tumour tissue is not evaluable for prospective central testing are not eligible.
    b. If multiple tumour specimens are submitted, patients may be eligible if at least one specimen is evaluable and positive for PD-L1 expression (regardless of whether the tissue is from an archival specimen or freshly collected relapsed disease).

        Acceptable samples include core needle biopsies for deep tumour tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

        Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

        Tumour tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.
10. Eastern Cooperative Oncology Group performance status 0-1.
11. Life expectancy ≥ 12 weeks.
12. Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment administration (Cycle 1, Day 1):
    a. Absolute neutrophil count (ANC) ≥ 1500 cells/μL (without granulocyte colony stimulating factor [G-CSF] support within 2 weeks prior to the first study treatment administration). G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1.
    b. Lymphocyte count ≥ 500/μL
    c. Platelet count ≥ 100,000/μL (patients may be transfused to meet this criterion. Following transfusion, a 14-day period is required before Cycle 1, Day 1)
    d. Haemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion. Following transfusion, a 14-day period is required before Cycle 1, Day 1)
    e. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 x the upper limit of normal (ULN), with the following exceptions:

        Patients with documented liver metastases: AST and ALT ≤ 5 x ULN

        Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 x ULN
    f. Serum bilirubin ≤ 1.5 x ULN

        Patients with known Gilbert's disease who have serum bilirubin level ≤ 3 x ULN may be enrolled.
    g. Patients who are not receiving therapeutic anticoagulation: international normalised ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Patients who are receiving an anticoagulant medicinal product must be on a stable anticoagulant regimen and have an INR which is not above the target therapeutic range during the 14 days preceding initiation of study treatment.
    h. Calculated creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault formula).
13. Negative human immunodeficiency virus (HIV) test at screening.

14. Negative hepatitis B surface antigen (HBsAg) test at screening.
15. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive HBcAb test followed by a negative hepatitis B virus (HBV) deoxyribonucleic acid (DNA) test at screening.

    The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive HBcAb test.

16. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV ribonucleic acid (RNA) test at screening.

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

17. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

    Women must remain abstinent or use contraceptive methods with a failure rate of ≤1% per year during the treatment period with any study treatment and for 5 months after the final dose of atezolizumab or 6 months after the last dose of capecitabine, whichever is later. Women must refrain from donating eggs during the same time period. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

    Examples of contraceptive methods with a failure rate of ≤ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

18. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

    With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of capecitabine or 6 months after the last dose of carboplatin/gemcitabine, whichever is later, to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Due to the possibility of irreversible infertility with carboplatin/gemcitabine, men receiving these chemotherapies should consult with their doctor regarding conservation of sperm prior to treatment initiation.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

For patients enrolled after the recruitment of all-comers is complete:

19. PD-L1-positive tumour status (assessed centrally prior to randomisation), defined as PD-L1 expression on tumour-infiltrating immune cells (IC) of 1% or greater (IC1/2/3).

Exclusion Criteria

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

Cancer-Specific Exclusion Criteria

1. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomisation
2. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.

   Patients with a history of treated CNS lesions are eligible, provided that all of the following criteria are met:

   a. Measurable or non-measurable disease, per RECIST v. 1.1, must be present outside the CNS
   b. No history of intracranial haemorrhage or spinal cord haemorrhage
   c. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
   d. There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
   e. The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 days prior to initiation of study treatment.
   f. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

      Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan

3. Symptomatic or rapid visceral progression
4. History of leptomeningeal disease
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) (patients with indwelling catheters such as PleurX® are allowed)
6. Uncontrolled tumour-related pain

   Patients requiring pain medication must be on a stable regimen at study entry.

   Symptomatic lesions (e.g. bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomisation. Patients should be recovered from the effects of radiation prior to study entry. There is no required minimum recovery period.

   Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g. epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to randomisation.

7. Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionised calcium or total calcium > 3 mmol/L or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

   Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

8. Malignancies other than TNBC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%) and treated with expected

curative outcome (such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)

General Medical Exclusion Criteria

9. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomisation, unstable arrhythmias, or unstable angina.

    Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimised in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

10. Presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second or third-degree heart block, evidence of prior myocardial infarction, or QT interval corrected using Fridericia's formula (QTcF) > 470 ms demonstrated by at least two consecutive ECGs.
11. Severe infection requiring oral or IV antibiotics within 4 weeks prior to randomisation, including but not limited to hospitalization for complications of infection, bacteraemia, or severe pneumonia.

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

12. Current treatment with anti-viral therapy for HBV.
13. Major surgical procedure within 4 weeks prior to randomisation or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis.

    Placement of central venous access catheter(s) (e.g. port or similar) is not considered a major surgical procedure and is therefore permitted.

14. Treatment with investigational therapy within 28 days prior to randomisation.
15. Pregnant or lactating or intending to become pregnant during or within 5 months after the last dose of atezolizumab, or within 6 months after the last dose of capecitabine, whichever is later.
16. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.

Exclusion Criteria Related to Atezolizumab

17. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins.
18. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the atezolizumab formulation.
19. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (refer to Appendix 5).

    Patients with the following are eligible:

    a. history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone.
    b. controlled Type 1 diabetes mellitus on a stable insulin dosing regimen.
    c. eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

- rash must cover less than 10% of body surface area.
- disease is well controlled prior to randomisation and only requires low potency topical steroids.
- no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral steroids).

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

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted
22. Active tuberculosis
23. Receipt of a live, attenuated vaccine within 4 weeks prior to randomisation or anticipation that a live, attenuated vaccine will be required during atezolizumab/placebo treatment or within 5 months after the last dose of atezolizumab/placebo
24. Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway targeting agents
25. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to randomisation
26. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, mycophenolate, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, or anticipated requirement for systemic immunosuppressive medications during the trial, with the following exceptions:

    Patients who have received acute, low dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

    Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled, or low-dose corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for this study.
27. Poor peripheral venous access
28. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, safety of participation, or interpretation of results. This includes significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome) or any other serious medical condition or abnormality in clinical laboratory tests that meet these criteria in the investigator's opinion.

<u>Exclusion Criteria Related to Capecitabine</u>

29. Inability to swallow pills
30. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis
31. Known dihydropyrimidine dehydrogenase (DPD) deficiency or history of severe and unexpected reactions to fluoropyrimidine therapy in patients selected to receive capecitabine
32. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine in patients selected to receive capecitabine. Use of these drugs is not allowed within 4 weeks of initiation of study treatment that includes capecitabine.
33. Hypersensitivity to any component of capecitabine drug formulation in patients selected to receive capecitabine.

Exclusion Criteria Related to Carboplatin/Gemcitabine

34. Hypersensitivity to platinum containing compounds or any component of carboplatin or gemcitabine drug formulations in patients selected to receive carboplatin and gemcitabine.

End of Study and Length of Study

The end of the study is defined as the last patient last visit (LPLV) *(regardless of whether the last patient last visit is for* a *patient who is part of the Global study or the China population)*. Global Study

Total study recruitment (of all-comers and additional patients with PD-L1-positive tumour status) is expected to occur over approximately 53 months.

This is an event driven trial. The clinical cut-off (CCO) date for the final OS analysis will be confirmed when the target number of mortality events (247 deaths) have occurred in the PD-L1-positive population, which is expected approximately 58 months after the first patient was randomised ("first patient in"; FPI) in the study.

The actual length of the study and the time for final analysis will depend on the actual recruitment rate and the number of events that occur. Mortality events will be monitored throughout the course of the study, and study timelines might be updated.

In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment may be eligible for continued (post-trial) access to atezolizumab.

China Population

The OS analysis for the China population will be conducted when approximately 49 deaths in the China population have been observed. The CCO date of OS analysis in the China population may be revisited according to the data maturity and estimated treatment effect from the global population.

Investigational Medicinal Products

Atezolizumab, placebo, carboplatin, gemcitabine and capecitabine are investigational medicinal products (IMPs) in this study. All IMPs will be provided by the study sponsor.

Test Product (Investigational Drug)

Atezolizumab is the test product in this study. Atezolizumab will be supplied as a sterile liquid in a single-use, 20 mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution. Atezolizumab will be administered at a dose of 1200 mg via IV infusion on Day 1 of each 3-week treatment cycle (Q3W). Administration of atezolizumab and placebo will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Comparator

Placebo is the comparator to the study test product (atezolizumab). Placebo will be identical in appearance to atezolizumab and is comprises the same excipients but without the atezolizumab drug product. It should be handled, stored, and administered in the same manner as atezolizumab (by IV infusion Q3W).

Chemotherapy Partner

Carboplatin, gemcitabine and capecitabine are chemotherapy partners in this study. For information on the formulation, packaging, and handling of these agents, refer to the local prescribing information.

Carboplatin and gemcitabine will be administered in combination as follows: gemcitabine 1000 mg/m^2, followed by carboplatin target AUC 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle. Day 8 gemcitabine administration should not occur earlier than Day 7 but can occur up to Day 11.

Capecitabine will be administered orally at a dose of 1000 mg/m^2 twice daily on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle.

Non-Investigational Medicinal Products

Non-investigational medicinal products (NIMPs) used in the study include premedication, medications that may be administered to manage AEs, and other permitted concomitant medications. All concomitant medications will be recorded.

Statistical Methods

Protocol version 4.0 introduced continuation of enrolment of approximately 190 additional (PD-L1-positive only) patients, after the recruitment of all-comers (PD-L1-positive and PD-L1-negative) has been completed.

Consequently, the main analysis populations are defined as follows:

- Modified intent-to-treat (mITT) population: all patients randomised in the study before protocol version 4.0 (referred to as all-comers, i.e., PD-L1-positive and PD-L1-negative), grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- Full Analysis Set (FAS) population: all patients randomised in the study, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- PD-L1-positive population: all patients randomised in the study whose PD-L1 status was IC1/2/3 at the time of randomisation, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- PD-L1-negative population: all patients randomised in the study whose PD-L1 status was IC0 at the time of randomisation, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.

Primary Analysis

The primary efficacy endpoint for this study, OS, is defined as the time from randomisation to death from any cause.

In order to control for the overall type I error at two-sided 5%, OS will be evaluated hierarchically in the following fixed order:

(1) OS in in the PD-L1-positive population (based on all patients randomised in the study whose PD-L1 status was IC1/2/3 at the time of randomisation),

(2) OS in the mITT population (based on all patients randomised in the study before protocol version 4.0),

with patients grouped according to their treatment assigned at randomisation.

Patients without a reported death event at the time of the analysis will be censored on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomisation +1 day.

OS will be compared between treatment arms based on the stratified log-rank test, using stratification factors provided at randomisation (as documented in the IxRS): presence of visceral (lung and/or liver) metastases (yes vs. no), tumour PD-L1 status (tumour-infiltrating immune cell [IC] 0 vs. IC1/2/3) and chemotherapy choice (carboplatin/gemcitabine vs. capecitabine). For OS in the PD-L1-positive population, presence of visceral metastases and chemotherapy choice will be used as stratification factors. The hazard ratio (HR) for death will be estimated using a stratified Cox regression model, using the same stratification factors as used for the log-rank test; HR estimate for treatment effect (addition of atezolizumab to chemotherapy versus chemotherapy alone) and corresponding two-sided 95% CI will be provided. Results from an unstratified analysis will also be provided as a sensitivity analysis.

Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

The CCO date for the primary endpoint analysis will take place when the required number of 247 mortality events have been reported in the PD-L1-positive population. This is projected to occur approximately 58 months after FPI. By this time-point, approximately 297 mortality events are expected to have occurred in the mITT population.

The OS analysis for the China population will be conducted when approximately 49 deaths in the China population have been observed. Assuming a hazard ratio of 0.7 for OS in the global population, the 49 OS events will provide approximately 75% probability of maintaining 50% of risk reduction compared to that estimated in the global population. The CCO date for OS analysis in the China population may be revisited according to the data maturity and estimated treatment effect from the global population.

Results from these analyses will be summarised in a separate report from the clinical study report (CSR) for the Global study.

Determination of Sample Size

Global Study

The primary objective of this study is to evaluate the efficacy of atezolizumab plus chemotherapy versus placebo plus chemotherapy in patients with early-relapsing (<12 months) inoperable *locally advanced or metastatic* TNBC as measured by OS.

Patients with TNBC whose disease has progressed within 12 months from their early breast cancer (eBC) treatment are typically excluded from treatment trials. However, retrospective analyses of OS in patients with triple-negative disease have found medians of 8 months (interquartile range: 3, 18) and approximately 11 months (interquartile range: 5, 20) in the relapsed vs de novo cohorts, respectively (den Brok et al. 2017). Notably, the TNBC populations in these studies included patients whose disease had progressed >12 months after (neo)adjuvant treatment. Based on these data in TNBC populations unselected for time to first relapse and the advice of clinical experts with active treatment practices that include patients with TNBC, an estimated median OS of 9.0 months was selected for the control arm of this study.

In order to control for the overall type I error at two-sided 5%, primary OS endpoint will be evaluated hierarchically in the following fixed order: (1) OS in the PD-L1-positive population; followed by (2) OS in the mITT population. A confirmatory test on (2) will only be conducted if the null-hypothesis for (1) has been rejected at two-sided 5% significance level.

Based on the estimated median OS of 9 months in the control arm, and a 1:1 randomisation ratio, 247 OS events are required to detect a target HR of 0.70 (3.8-month improvement in median OS) with the addition of atezolizumab to chemotherapy, with 80% power by two-sided log-rank test at an alpha level of 0.05. The expected study recruitment rate is approximately 20 all-comer patients per month, and approximately 37% of all-comers were found to be PD-L1-positive. Following the enrolment of 382 all-comer patients, subsequent recruitment will continue only in patients with PD-L1-positive tumour status, for approximately 190 additional patients randomised in order to achieve the target sample size of 330 patients and the required number of 247 events for the primary OS analyses in PD-L1 positive population.

The overall study population is estimated at approximately 572 patients (382 all-comers plus approximately 190 additional patients with PD-L1-positive tumour status).

China Population:

After approximately 572 patients have been randomised in the Global study, global recruitment will be closed. Additional patients with PD-L1-positive tumour status may be subsequently randomised in China only, following the same randomisation procedures and ratio (1:1), for a total enrolment of

approximately 70 patients with PD-L1-positive tumour status in mainland China (including patients from China enrolled in the Global study).

The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in the China population (enrolled in the Global study and during additional recruitment in China) is consistent with the efficacy observed in the global population (Global study).

Interim Analyses

No interim analyses of efficacy are planned. An iDMC will be in place for the periodic review of safety data.

Full details of the planned study analyses will be presented in the SAP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ADA	anti-drug antibody, also known as anti-therapeutic antibody
AUC	area under the concentration-time curve
BC	breast cancer
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBR	clinical benefit rate
CCO	clinical cut-off
CD	cluster of differentiation
C-DoR	duration of response for confirmed responders
CLS	capillary leak syndrome
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CNS	central nervous system
COVID	coronavirus disease
COPD	chronic obstructive pulmonary disease
C-ORR	confirmed objective response rate
CR	complete response
CrCl	creatinine clearance
CRO	Contract Research Organisation
CRS	cytokine-release syndrome
CT	computed tomography
ctDNA	circulating tumour deoxyribonucleic acid
CU	compassionate use
DNA	deoxyribonucleic acid
DoR	duration of objective response

Abbreviation	Definition
DPD	dihydropyrimidine dehydrogenase
DRB	Data Review Board
eBC	early breast cancer
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ECG	electrocardiogram
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
ER	(o)estrogen receptor
ESMO	European Society for Medical Oncology
ESO	European School of Oncology
EQ-5D-5L	European Quality of Life 5 Dimension, 5-level version
FAS	Full Analysis Set
FFPE	formalin-fixed paraffin-embedded
FoxP3	Forkhead Box P3 protein (scurfin)
FPI	first patient in
5-FU	5-fluorouracil
G-CSF	granulocyte colony-stimulating factor
GHS	Global Health Status
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HGRAC	Human Genetics Resources Administration of China
HR	hazard ratio
HUS	Haemolytic-uraemic syndrome
IC	immune cell
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Centre
iDMC	independent Data Monitoring Committee
IHC	Immunohistochemistry
Ig	Immunoglobulin
IL	Interleukin
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug application
INR	International Normalised Ratio
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	Intent-to-treat
IxRS	interactive voice/web response system
LDH	lactate dehydrogenase
LMWH	low-molecular weight heparin
LPLV	last patient last visit
LS	least squares
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MDS	myelodysplastic syndrome
MID	minimally important difference
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
NaCl	sodium chloride
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
NK	natural killer (cell)
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PCR	polymerase chain reaction
PD	Progression of disease / disease progression
PD−1	programmed death−1
PD−L1	programmed death−ligand 1
PET	positron emission tomography
PFS	progression-free survival
PIN	personal identification number
PK	pharmacokinetic

Abbreviation	Definition
PRES	posterior reversible encephalopathy syndrome
PR	progesterone receptor/partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PVC	polyvinylchloride
QoL	quality of life
QLQ-BR23	breast cancer module for QLQ-C30
QLQ-C30	Quality of Life Questionnaire Core 30
Q3W	every three weeks
RBC	red blood cell
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SCAR	severe cutaneous adverse reaction
SD	stable disease/standard deviation
SLE	systemic lupus erythematosus
SIRS	systemic inflammatory response syndrome
SNP	Single Nucleotide Polymorphism
TEN	toxic epidermal necrolysis
TILs	tumour infiltrating lymphocytes
TLS	tumour lysis syndrome
TNBC	triple-negative breast cancer
TNF	tumour necrosis factor
TSH	thyroid-stimulating hormone
TTD	time to deterioration
T3	triiodothyronine
T4	thyroxine
ULN	upper limit of normal
USP	United States Pharmacopeia
WBC	white blood cell
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer (BC) is the second most common cancer in the world and, by far, the most frequent cancer among women both in more and less developed regions. There were an estimated 1.67 million new cancer cases diagnosed worldwide in 2012 (25% of all cancers) (Ferlay et al. 2013; Ferlay et al. 2015; Torre et al. 2015). Age-adjusted incidence rates (per 100,000 population) are highest in North America (91.6), followed by Europe (69.9), Latin America (47.2), and Eastern Asia (27.0) (Ferlay et al. 2013). In the United States, there was a statistically significant increase of 0.4% (95% Confidence Interval [CI]: 0.1% to 0.8%) per year between 2009 and 2014 in breast cancer incidence (Jemal et al. 2017), and it is projected that there will be 255,180 new diagnoses due to BC (Siegel et al. 2017). An estimated 3,560,570 women were living with BC in the United States in 2016 (Miller et al. 2016). In Europe, BC accounts for 28.8% of female cancer and is estimated to affect more than one in 10 women (Lundqvist et al. 2016). In five Latin American countries, the estimated incidence rates for BC were between 27.2 and 74.0 per 100,000 women in 2008 (Nigenda et al. 2016). The majority of patients are diagnosed with localised breast cancer; however, approximately 6% of patients present with de novo metastatic disease and between 10% and 40% of patients with localised breast cancer will relapse systemically (Zeichner et al. 2015a; Zeichner et al. 2015b).

Breast cancer ranks as the fifth cause of death from cancer overall in the world (522,000 deaths; 6.4% of all cancer-related deaths), the leading cause of cancer-related deaths in women (14.7% of all cases), and the second cause of cancer death in women in more developed regions (198,000 deaths, 15.4% of total) after lung cancer (Ferlay et al. 2013; Ferlay et al. 2015; Torre et al. 2015). Age-adjusted mortality rates (per 100,000 population) are highest in Europe (16.1), followed by North America (14.8), Latin America (13.0), and Eastern Asia (6.1) (Ferlay et al. 2013). In the United States, death rates due to breast cancer decreased by 1.6% (95% CI: –1.8% to –1.4%) per year between 2009 and 2014 (Jemal et al. 2017), and it is projected that there will be 41,070 deaths due to BC in 2017 (Siegel et al. 2017). Five-year relative survival rates for BC cases diagnosed between 2006 and 2012 were 90.8% (95% CI: 90.5% to 91.1%) (Jemal et al. 2017). In five Latin American countries, the estimated mortality rates for BC were between 10.0 and 20.1 per 100,000 women in 2008 (Nigenda et al. 2016).

The above statistics include all subtypes of BC (Ferlay et al. 2013; Collignon et al. 2016). However, BC is a heterogeneous disease encompassing about 15 different types of carcinomas, which are for therapeutic reasons, further classified according to their oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status (Brouckaert et al. 2012). These subgroups have important implications for the choice of therapy, treatment outcomes, recurrence rate, and mortality risk. The lack of expression of ER, PR, and HER2 is referred to as triple-negative BC (TNBC) (Trivers et al. 2009; Zeichner et al. 2016).

The prognosis of patients with metastatic breast cancer (mBC) varies from several months to many years depending upon multiple factors, including, but not limited to, ER/PR status and HER2 status (Zeichner et al. 2015a; Zeichner et al. 2015b). Between 1975 to 1977 and 2006

to 2012, five-year relative survival for distant-stage BC increased from 18.7% (95% CI: 16.9% to 20.6%) to 33.6% (95% CI: 32.2% to 35.0%) for female breast cancer (Jemal et al. 2017). However, most new treatment options for mBC are only effective for ER/PR-positive or HER2-positive metastatic tumours (Zeichner et al. 2016).

1.1.1 Triple-Negative Breast Cancer (TNBC)

The triple-negative subtype is a heterogeneous group of BCs, characterised by the lack of expression of hormonal receptors and the absence of HER2 overexpression (Collignon et al. 2016). According to the St. Gallen International Expert Consensus (Goldhirsch et al. 2009), and the recommendations of the American Society of Clinical Oncology and the American College of Pathology (Hammond et al. 2010; Allison et al. 2020), tumour specimens are ER or PR negative if less than 1% of tumour cells express the oestrogen and progesterone receptors via immunohistochemistry (IHC), and HER2-negative if showing IHC 0 or 1+ or in situ hybridization (ISH) negative using single-probe ISH or dual-probe ISH (Wolff et al. 2018). Should these definitions be revised by clinical experts during the course of the study, the updated definitions may be adopted as part of a protocol amendment.

Approximately 15%–20% of all BCs belong to the triple-negative phenotype that has distinct risk factors, distinct molecular features, and a particular clinical presentation and outcome (Brouckaert et al. 2012; Lin et al, 2012; Penault-Llorca and Viale, 2012). The TNBC phenotype has been associated with Black race, younger age, and more advanced tumour stage at presentation (Millikan et al. 2008; Lund et al. 2009; Trivers et al. 2009; Lin et al, 2012; Danforth 2013). TNBCs are more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with metastatic TNBCs exhibit rapid progression and a poor clinical outcome (Mersin et al. 2008; Trivers et al. 2009; Wahba and El-Hadaad, 2015). TNBC is associated with a higher risk of brain or lung metastases, and worse breast cancer-specific and overall survival (OS) (Lin et al, 2012); median OS is generally between 13 months (Kassam et al. 2009) and 17.5 months in patients treated with various chemotherapy agents (Roche data on file).

Large-scale comprehensive genomic analyses have characterised the heterogeneous nature of TNBCs and their diverse gene-expression patterns and underlying genomic changes, but these insights have not yet provided clear guidance for the identification of clinically effective targeted therapies (Hirshfield and Ganesan, 2014). Chemotherapy is the mainstay of treatment of TNBC, and current treatment strategies for triple-negative disease include anthracyclines, taxanes, ixabepilone, platinum agents, and bevacizumab (Hudis and Gianni, 2011). However, although TNBC may respond to chemotherapy, including taxanes, relatively few new agents have been approved for the subset of patients with metastatic TNBC (mTNBC) (Carey et al. 2012; O'Shaughnessy et al. 2014; Hirshfield and Ganesan, 2014; Zeichner et al. 2016) and there are no targeted therapies with widespread global approval available for patients with this specific subtype of breast cancer. Therefore, there is a pressing need for clinically active agents for mTNBC.

1.1.2 Treatment of Metastatic Breast Cancer

The treatment algorithm for patients with mBC is based on several factors that include clinical, pathologic, and histologic characteristics such as the presence or absence of HER2 amplification; hormone receptor status; prior response to and/or failure of hormonal agents; number and specific sites of metastatic disease; and treatment history in both the metastatic

and adjuvant settings (Piccart-Gebhart et al. 2008). Treatment options for mBC include endocrine therapies, monoclonal antibodies, antibody-drug conjugates, targeted therapies and different types of chemotherapy (Hernandez-Aya and Ma, 2016). Several cytotoxic chemotherapy agents have shown activity in mBC, including anthracyclines, taxanes, gemcitabine, capecitabine, vinorelbine, eribulin, and ixabepilone. The response rates and progression-free intervals observed with these agents vary depending on the extent and type of prior therapy and extent of metastatic disease, as well as the biology of the disease (Piccart-Gebhart et al. 2008).

However, despite striking discoveries and a broad therapeutic armamentarium, mBC remains incurable. The goal of treatment of mBC is to prolong survival and to improve quality of life by mitigating cancer-related symptoms without increasing toxicity (Hernandez-Aya and Ma, 2016).

1.1.2.1 Platinum-based Regimens in Metastatic Breast Cancer

As predicted by their deoxyribonucleic acid (DNA)-damaging mechanism of action, platinum compounds are expected to be particularly active in tumours characterised by a defect in DNA double-strand break repair, such as those without active breast cancer susceptibility gene (BRCA1/2) proteins (Turner and Tutt 2012; Cardoso et al. 2014; Isakoff et al. 2015). In recent years, substantial evidence has accumulated confirming the link between TNBC and BRCA1/2 mutations (Gerratana et al. 2016; González-Rivera et al. 2016). Approximately 80% of breast cancers with BRCA1 mutation are TNBCs, and up to 20% of patients affected by TNBC are carriers of a BRCA germline mutation. Therefore, TNBCs had been postulated to be particularly sensitive to interstrand cross-linking agents, including platinum analogues (Turner and Tutt 2012; Isakoff et al. 2015; Gerratana et al. 2016).

The clinical activity of first- or second-line platinum monotherapy in mTNBC was demonstrated in a multicentre Phase II clinical trial (TBCRC009; N=86). In this study, objective response rate (ORR) was 25.6% overall (cisplatin and carboplatin groups combined), and 54.5% in patients with germline BRCA1/2 mutations (p=0.022) (Isakoff et al. 2015). In the recent phase III randomised TNT trial (N=376), treatment with carboplatin resulted in a significantly higher ORR versus docetaxel in patients with BRCA1/2 mutations (68% vs. 33.3%; P = 0.03) (Tutt et al. 2014).

Platinum-containing chemotherapy combinations have demonstrated activity in patients with TNBC both in the neoadjuvant (Alba et al. 2012; von Minckwitz et al. 2014; Sikov et al. 2015) and metastatic settings (O'Shaughnessy et al. 2011; O'Shaughnessy et al. 2014; Yardley et al. 2015), particularly in TNBC patients with BRCA1/2 mutations (Tutt et al. 2014; Telli et al. 2015). In the single-arm phase II PrECOG 0105 study, 80 patients with stage I to IIIA (T ≥ 1 cm) TNBC or BRCA1/2 mutation-associated breast cancer received neoadjuvant gemcitabine (1,000 mg/m^2 intravenously [IV] on days 1 and 8), carboplatin (area under curve [AUC] of 2 IV on days 1 and 8), and iniparib (5.6 mg/kg IV on days 1, 4, 8, and 11) every 21 days for initially four, and following a protocol amendment, every 6 cycles. In the intent to treat (ITT) population, pathological complete response (pCR) rates were higher in patients with BRCA1/2 mutation (47%), and even higher in patients with TNBC and BRCA1/2 mutations (56%) compared to those who were not carriers of these mutations (Telli et al. 2015).

In a phase II randomised study (n = 123) evaluating the clinical benefits of gemcitabine and carboplatin with or without iniparib in patients with metastatic TNBC, gemcitabine 1000 mg/m^2 IV plus carboplatin IV dosed at AUC2 on Days 1 and 8 every 3 weeks (n = 62) resulted in a median progression-free survival (PFS) of 3.6 months, a median OS of 7.7 months, and ORR of 32% (O'Shaughnessy et al. 2011). In a subsequent confirmatory randomised Phase III study comparing these two regimens in 519 women with metastatic TNBC, gemcitabine plus carboplatin demonstrated median PFS and OS of 4.1 and 11.1 months, respectively in the ITT population and 4.6 and 12.4 months based on an exploratory analysis in patients receiving first-line treatment (O'Shaughnessy et al. 2014).

Other gemcitabine and carboplatin-containing regimens have also been evaluated in patients with advanced TNBC. Combining panitumumab with gemcitabine and carboplatin in 71 women with metastatic TNBC resulted in a median PFS of 4.4 months and ORR of 42% (Yardley et al.2015). The combination of carboplatin with eribulin (a mitotic inhibitor) as first≤line therapy for locally recurrent or metastatic TNBC resulted in ORR of 57.9%, clinical benefit rate (CBR) of 68.1%, and a median PFS of 8.4 months (95% CI: 4.6 to 10.4) in a recently reported Phase II study (Michalaki et al. 2016). The Phase II/III tnAcity study comparing weekly nab-paclitaxel 125 mg/m^2 plus gemcitabine IV 1000 mg/m^2 or carboplatin IV AUC2 versus gemcitabine/carboplatin as first-line treatment of patients with metastatic TNBC is currently ongoing (Yardley et al.2015), and the results of the Phase II part (n=191) have recently been reported. Weekly nab-paclitaxel plus carboplatin was associated with significantly longer PFS (7.4 months) compared to weekly regimens of either nab-paclitaxel plus gemcitabine (5.4 months; P=0.02; HR=0.60, 95% CI: 0.39 to 0.93) or of carboplatin plus gemcitabine (6.0 months; P= 0.03; HR=0.61, 95% CI: 0.39 to 0.94). Nab-paclitaxel plus carboplatin also prolonged OS (16.4 months) compared to either nab-paclitaxel plus gemcitabine (12.1 months; P=0.07; HR=0.66, 95% CI: 0.42 to 1.04) or of carboplatin plus gemcitabine (12.6 months; P= 0.18; HR=0.74, 95% CI: 0.48 to 1.16); however, the between-group differences were not statistically significant (Yardley et al.2016).

A recent systematic review and meta-analysis of 23 randomised trials involving 4625 patients assessed the efficacy and safety of platinum therapy (11 with cisplatin, 11 with carboplatin, and 1 with either agents respectively) in patients with locally advanced or metastatic breast cancer. Although at the expense of significantly increased fatigue, haematological and gastrointestinal toxicity, compared with non-platinum regimens, cisplatin, and carboplatin prolonged OS (HR=0.91, 95% CI: 0.83 to 1.00, p = 0.04), PFS (HR=0.84; 95% CI: 0.73 to 0.97, p = 0.01), and RR (HR=1.27, 95% CI: 1.03 to 1.57, p = 0.03) (Petrelli et al. 2016).

According to the latest (2nd) revision of the European School of Oncology (ESO)- European Society of Medical Oncology (ESMO) international consensus guidelines for advanced breast cancer, in patients with BRCA-associated triple-negative or endocrine-resistant metastatic breast cancer previously treated with an anthracycline and a taxane (in the adjuvant or metastatic setting), a platinum regimen may be considered (Cardoso et al. 2014).

1.1.2.2 Capecitabine in Metastatic Breast Cancer

Capecitabine is approved for the treatment of locally advanced or metastatic breast cancer: (i) in combination with docetaxel after failure of prior anthracycline-containing therapy; and (ii) as monotherapy after failure of taxanes and an anthracycline-containing chemotherapy regimen, or in patients for whom further anthracycline therapy is not indicated. The

recommended dose of capecitabine is 1250 mg/m^2 or 1000 mg/m^2 administered orally twice daily (morning and evening) for 2 weeks, followed by a 1-week rest period, given as 3-week cycles (Capecitabine SmPC; NCCN Breast Cancer Guideline v2, 2017).

The efficacy and safety of capecitabine-containing regimens in advanced TNBC has been evaluated in several recent prospective clinical trials. In patients with anthracycline- and taxane resistant metastatic TNBC, combination of ixabepilone and capecitabine improved ORR and PFS compared to capecitabine alone (ORR 27% vs. 9%; PFS 4.1 vs. 2.1 months, respectively) (Pivot et al. 2009). In a pilot trial evaluating the efficacy of a metronomic schedule of doxorubicin, cyclophosphamide and capecitabine in locally advanced and metastatic TNBC, the ORR was 58%, 29.4% of patients achieved a pCR, and in patients with metastatic disease, median PFS was 8.3 months (Skrypnikova et al. 2011). The combination of oral capecitabine with cyclophosphamide was found to be an effective first- or second-line therapy for metastatic BC, demonstrating high activity in both luminal A and triple-negative disease: ORR was 44.4%, CBR was 57.8%, median PFS was 12.3 months (10.7 months in triple-negative disease), and the 1- and 2-year survival rates were 86 and 71%, respectively. (Yoshimoto et al. 2012). In another study of 53 patients with metastatic TNBC, first-line treatment with capecitabine plus docetaxel resulted in ORR of 15.4%, PFS of 4.8 months, and OS of 21.5 months (Fan et al.2013). In an open-label pilot study involving 45 patients with metastatic TNBC, combination treatment with capecitabine and docetaxel, or capecitabine and vinorelbine was associated with a total ORR of 20%, CBR of 40%, PFS of 5.2 months, and OS of 18.2 months (Liao et al, 2013). Treatment with capecitabine plus cisplatin in 33 patients with metastatic TNBC pre-treated with anthracyclines and taxanes resulted in ORR of 63.6%, median PFS of 8.2 months (10.8 months in responding patients), and median OS of 17.8 months (25.8 months in responding patients) (Li et al. 2015).

In the Phase III randomised RIBBON-2 study compared the efficacy and safety of bevacizumab combined with standard chemotherapy regimens versus chemotherapy alone as second-line treatment of HER2-negative metastatic breast cancer, physician-selected chemotherapy was a taxane for 304, gemcitabine for 160, capecitabine for 144, and vinorelbine for 76 patients. For patients who received taxane, gemcitabine, or capecitabine, PFS favoured combination with bevacizumab (HR, 0.64, 0.90, and 0.73, respectively), with no statistically significant difference between these three cohorts (Brufsky et al. 2011). Of the 684 patients treated in RIBBON-2, 159 (23%) had TNBC, and the majority were treated with a taxane (Brufsky et al. 2012).

Lastly, after initial disease control was achieved with capecitabine plus docetaxel combination chemotherapy in 55 mTNBC patients, capecitabine maintenance therapy (compared to no maintenance) was shown to significantly prolong median PFS time (10.1 vs. 6.7 months, respectively; P=0.032) (Liang et al. 2014).

1.1.2.3 PD-L1 Inhibitors in the Treatment of TNBC

Investigations of targeted therapy for advanced TNBC includes immune checkpoint inhibitors targeting the programmed death receptor 1 (PD-1)/ programmed death ligand 1 (PD-L1; also called B7-H1 or cluster of differentiation [CD]274). PD-L1 is expressed on many cancer and immune cells (ICs; e.g., macrophages), and plays an important part in blocking the 'cancer immunity cycle' by binding and stimulating PD-1 and B7.1 (CD80), both of which are negative regulators of T-lymphocyte activation. PD-1 is an inhibitory receptor expressed on T cells

following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008; Herbst et al. 2014). B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation, and secretion of cytotoxic mediators, and restricts tumour cell killing, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011; Herbst et al. 2014). The PD-1/PD-L1 pathway has been implicated in tumours evading immune surveillance. Blockage of the PD-1/PD-L1 interaction enables the rapid restoration of the effector function of preexisting anticancer T cells (Chen and Mellman, 2013; Saha and Nanda, 2016). Blocking PD-L1 should therefore enhance anticancer immunity (Herbst et al. 2014).

Based on available clinical evidence, blockade of the PD-1/PD-L1 axis with atezolizumab (Tecentriq®) (Emens et al. 2015; Adams et al. 2015; Schmid et al. 2017; Schmid et al. 2018; Schmid et al. 2020), *or* pembrolizumab (Keytruda®) (Nanda et al. 2016; Adams et al. 2017a; Adams et al. 2017b; Cortes et al. 2020; Rugo et al. 2021), is a viable treatment strategy in patients with advanced TNBC.

1.2 BACKGROUND ON ATEZOLIZUMAB

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

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

Atezolizumab (Tecentriq) is approved in several countries around the world for the treatment of urothelial carcinoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), triple-negative breast cancer (TNBC), hepatocellular carcinoma, and melanoma.

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

1.2.1 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behaviour, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were, thus, undertaken with atezolizumab.

The safety, PK, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab with cynomolgus monkey and human

PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

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

1.2.2 Summary of Clinical Studies in Patients with TNBC

Atezolizumab is being investigated in multiple Phase I, II, and III clinical studies, both as monotherapy and in combination with several anti-cancer therapies against solid tumours and haematologic malignancies (see the Atezolizumab Investigator's Brochure for study descriptions).

Anti-tumour activity, as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 response, has been observed across multiple advanced tumour types for both atezolizumab monotherapy as well as in combination with bevacizumab and/or chemotherapy; refer to the Atezolizumab Investigator's Brochure for details. In patients with mTNBC, atezolizumab has shown activity as monotherapy (Emens et al. 2015; Schmid et al. 2017), and in combination with nab-paclitaxel (Adams et al. 2016; Schmid et al. 2018; Schmid et al. 2019; Emens et al. 2021). Combining atezolizumab with chemotherapy is hypothesised to enhance tumour-specific T-cell immunity by exposing the immune system to high levels of chemotherapy-induced tumour antigens and modulating T-cell and NK cell functions (Adams et al. 2016).

1.2.2.1 Efficacy of Atezolizumab Monotherapy in Patients with TNBC

Atezolizumab monotherapy has been evaluated in a mTNBC expansion cohort as part of a multicentre Phase Ia Study PCD4989g (clinicaltrials.gov identifier: NCT01375842). PCD4989g is a first-in-human, ongoing open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, PK, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent to patients with locally advanced or metastatic solid malignancies or haematologic malignancies. Atezolizumab is administered at 15 mg/kg, 20 mg/kg, or 1200 mg flat dose IV every three weeks (Q3W). As of 31 December 2016, there were 116 patients enrolled in the PCD4989g study. Among 115 ORR-evaluable patients, investigator-assessed confirmed ORR was 10% (95% CI: 5 to 16) with 3 complete responses (CR) and 8 partial responses (PR). Median duration of objective response (DoR) was 21 months (range 3 to >38 weeks) and all-patient median OS was 8.9 months (95% CI: 7.0 to 12.6), with a median follow-up duration of 25.3 months. Median duration of objective response was 21.1 months (range 9.6 weeks to non-estimable [NE]) and all-patient median OS was 8.9 months (95% CI: 7.0 to 12.6), with a median follow-up duration of 25.3 months. Median progression-free survival (PFS) was 1.4 months (95% CI: 1.4 to 1.6). These data suggest a similarity to or advantage over standard of care (SOC) treatment. Higher PD-L1 expression (IC2/3) compared to lower PD-L1 expression (IC0/1) was associated with better clinical outcomes, as evidenced by higher ORR (12% vs. 5% in the two subgroups, respectively), and longer median OS (10.5 months [95% CI: 7.1 to

14.7] vs. 7.0 [95% CI: 5.1 to 12.6], respectively). Greater treatment benefit was also observed in patients receiving first-line (1L) compared to subsequent lines (2L+) of atezolizumab treatment, as evidenced by higher ORR (24% among 1L patients vs. 6% among 2L+ patients), and longer median OS (17.6 months [95% CI: 10.1 to NE], vs. 7.3 months [95% CI: 6.1 to 10.8], respectively). Median PFS was consistent (approximately 1.4 months) regardless of PD-L1 expression or line of therapy; refer to the Atezolizumab Investigator's Brochure for further details. Atezolizumab increased intratumoural tumour infiltrating lymphocytes (TILs), CD8, macrophages and IC PD-L1 expression, but no response association was observed (Schmid et al. 2017).

1.2.2.2 Safety of Atezolizumab Monotherapy

Pooled safety data for atezolizumab monotherapy are available for 3178 patients who were treated with single-agent atezolizumab in eight studies. The majority of patients (over 97%) received atezolizumab at a dose of 1200 mg Q3W. Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined. Grade 3-4 adverse events occurred in 46.5% of patients, and Grade 5 adverse events in 3.8% of patients. Adverse events led to treatment discontinuation in 7.1% of patients, and to dose interruption in 27.7% of patients. The most commonly reported adverse events (≥ 10%) include fatigue (35.9%), decreased appetite (25.5%), nausea (23.5%), cough (20.8%), dyspnoea (20.5%), constipation (20.5%), pyrexia (20.1%), diarrhea (19.6%), anemia (15.9%), back pain (15.3%), vomiting (15.1%), asthenia (14.5%), arthralgia (13.9%), pruritus (12.6%), rash (11.3%), headache (11.0%), urinary tract infection (10.6%), and peripheral edema (10.4%); refer to the current Atezolizumab Investigator's Brochure for details.

As of the all-indication data cut-off date of 31 December 2016, safety information was available for 658 safety-evaluable patients from all lines of therapy in the PCD4989g study, including 116 patients with TNBC. The median age of the 658 safety-evaluable patients was 61 years (range 20 to 89 years); 79% were White, and approximately half (53%) were male. Approximately one-third (35%) of the patients received 1200 mg Q3W of atezolizumab (PCD4989g Clinical Study Report, Roche Data on File).

Adverse Events in the mTNBC Subpopulation of Study PCD4989g

Of the 116 safety-evaluable patients with TNBC, 114 patients (98.3%) reported one or more adverse event. A total of 59 (50.9%) patients experienced Grade 3–4 adverse events based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE). Treatment-related Grade 3–4 events occurred in 13 (11.2%) of patients. Serious adverse events were reported for 51 patients (44.0%). Grade 5 adverse events (not including deaths due to cancer progression) occurred in three patients (2.6%). Adverse events led to atezolizumab discontinuation in 5 (4.3%) patients (PCD4989g Clinical Study Report, Roche Data on File).

Long-term follow-up data from 115 safety-evaluable patients in Study PCD4989g (data cut-off 31 March 2016) indicated that atezolizumab was generally well tolerated, with no new safety signals detected (Schmid et al. 2017).

Safety findings in the TNBC cohort of Study PCD4989g are consistent with those observed in the overall study population. Refer to the Atezolizumab Investigator's Brochure for further details.

Adverse Events in the Overall Population of Study PCD4989g

Almost all (98.6%) of the 658 safety-evaluable patients reported at least one adverse event. The most common adverse events (occurring in ≥ 20% of patients) included fatigue (40.6%), nausea (29.0%), decreased appetite (26.6%), diarrhoea (22.5%), constipation (22.0%), pyrexia (21.9%), dyspnoea (21.7%), cough (20.7%), vomiting (20.5%), and anaemia (20.1%). Other adverse events reported ≥10% of patients included back pain, headache, asthenia, arthralgia, pruritus, rash, abdominal pain, oedema peripheral, insomnia, dizziness, upper respiratory tract infection, chills, and urinary tract infection. Treatment-related adverse events (per investigator's assessment of causality) were reported in 444 patients (70.6%).

Approximately half of the 658 patients (51.5%) experienced Grade 3–4 adverse events, most commonly anaemia (5.6%), dyspnoea (4.6%), hyponatraemia (4.4%), fatigue (3.2%), dehydration (2.4%), asthenia (2.3%), and hyperglycaemia and abdominal pain (2.0% each). Treatment-related Grade 3–4 events were reported in 95 (14.4%) of patients, with AST increased, asthenia, and anaemia (1.2% each), dyspnoea (1.1%), and hyponatremia (0.9%) as the most frequently occurring.

The rate of serious adverse events was 43.6%, with the most common (≥24 patients or 3.6%) being dyspnoea (3.6%), pyrexia (3.0%), and UTI (2.0%). Ten patients (0.5%) experienced Grade 5 adverse events (not including deaths due to cancer progression), including three events considered as related to atezolizumab: hepatic failure (in the NSCLC cohort), and death (not otherwise specified) and pulmonary hypertension (both in the TNBC cohort). Adverse events led to atezolizumab discontinuation in 30 (4.6%) patients; of these, hypoxia, pneumonitis, sepsis, and pyrexia were reported in two patients (0.3%) each; the remaining events were single occurrences (PCD4989g Clinical Study Report, Roche Data on File).

Immune-Mediated Adverse Events

The safety data presented in this section is based on pooled data from 3178 patients with multiple tumour types and supporting data from the estimated cumulative exposure in >23,000 patients across all clinical trials. The overall immune-mediated adverse drug reaction (ADR) rate for atezolizumab monotherapy is 12.7%, the majority of which were Grade 1–2 immune-mediated ADRs (Atezolizumab Investigator's Brochure).

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. Important identified risks associated with atezolizumab include the occurrence of the following immune-mediated adverse events (listed with total frequencies of these events in pooled clinical trials of atezolizumab monotherapy): immune-mediated pneumonitis (2.7% [87/3178]); immune-mediated hepatitis (2.0% [62/3178]); immune-mediated colitis (1.1% [34/3178]); immune-mediated pancreatitis (0.6% [18/3178]); immune-mediated endocrinopathies, including diabetes mellitus (0.3% [11/3178]),

hypothyroidism (5.2% [164/3178]), hyperthyroidism (0.9% [30/3178]), and adrenal insufficiency (0.4% [12/3178]); immune-mediated hypophysitis (<0.1% [2/3178]); immune-mediated neuropathies, including Guillain-Barré syndrome (0.2% [5/3178]) and myasthenic syndrome/myasthenia gravis (<0.1%); immune-mediated meningoencephalitis (0.4% [13/3178]); immune-mediated myocarditis (<0.1%); immune-mediated nephritis (<0.1% [3/3178], including one case of Henoch-Schoenlein purpura nephritis); and immune-mediated myositis (0.4% [12/3178]); in addition, there have been 34 cases of infusion-related reactions (1.1%). Overall, the nature and frequency of immune-mediated adverse events has been consistent across multiple tumour types in clinical studies of atezolizumab.

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

Treatment-emergent (treatment-induced plus treatment-enhanced) anti-drug antibodies (ADAs) have been observed in the clinical trials of atezolizumab, at doses of 10 mg/kg and above. In the monotherapy all patient population, the post-baseline incidence of treatment-emergent atezolizumab ADA (treatment induced and enhanced) was 37.0% (1002/2705). In the monotherapy all patient population, the incidence of all grade adverse events, Grade 5 adverse events, adverse events leading to treatment withdrawal, adverse events leading to dose interruption and adverse events of special interest (AESI) was similar irrespective of post-baseline ADAs status (negative or positive). The incidence of serious adverse events and Grade 3–4 adverse events was increased in ADA-positive compared with ADA-negative patients (SAEs: 42.4% vs. 37.6%, respectively; Grade 3–4 AEs 49.1% vs. 44.3%, respectively); however, none of these events were driven by any specific System Organ Class or individual adverse event. In the monotherapy all patient population, the incidence of hypersensitivity events and infusion related reactions was low and consistent between ADA-positive and ADA-negative patients.

Refer to the Atezolizumab Investigator's Brochure for additional details and current updates regarding clinical safety.

1.2.2.3 Efficacy of Atezolizumab Combined with Chemotherapy in Patients with TNBC

mTNBC Subpopulation of Study GP28328

Building on the promising results of atezolizumab as a single agent, an open-label Phase Ib trial (GP28328; clinicaltrials.gov identifier: NCT01633970) was initiated to evaluate atezolizumab in combination with chemotherapy and/or bevacizumab in locally advanced or metastatic solid tumours. One of the arms (Arm F; n=33) is evaluating 4-week cycles consisting of atezolizumab 800 mg Q2W (Days 1 and 15) in combination with nab-paclitaxel 125 mg/m^2 Q1W (Days 1, 8, and 15) in patients with mTNBC, treated with ≤2 prior lines of therapy for metastatic disease. After nab-paclitaxel discontinuation, maintenance atezolizumab is allowed until loss of clinical benefit. Primary endpoints are safety and tolerability; secondary endpoints include clinical activity. Preliminary results are available for the 32 enrolled female patients aged 32 to 84 years (median 56 years). The majority of patients (87%) received prior taxane therapy (Adams et al. 2015; Adams et al. 2016). As of the data cut-off of 14 January 2016, the investigator-assessed ORR per RECIST v1.1 was 37.5% (95% CI: 21.1 to 56.3; confirmed responses only); these included one complete CR and 11 PRs. Clinical benefit was observed across all lines of therapy, with ORRs being

comparable between patients with one vs three or more previous lines of treatment (46.2% and 40.0%, respectively); refer to the Atezolizumab Investigator's Brochure for further details.

Results of Study WO29522 (IMpassion130)

Based on the tolerability and promising activity of atezolizumab in mTNBC, the combination of atezolizumab and nab-paclitaxel has been evaluated in a global, randomised, placebo-controlled Phase III study (WO29522/IMpassion130 study; ClinicalTrials.gov identifier: NCT02425891) in previously untreated unresectable locally advanced or metastatic TNBC patients (N=902). Eligible patients were randomised in a 1:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Pre-specified co-primary efficacy endpoints include investigator-assessed PFS by RECIST v1.1 (in the ITT and PD-L1−positive population), and OS (in the ITT and PD-L1−positive population).

A total of 902 patients were randomised in the study; 451 in each group. In the atezolizumab plus nab-paclitaxel and placebo plus nab-paclitaxel groups, respectively, median age was 55 and 56 years, respectively; 57% and 60%, respectively had ECOG performance status of 0 and 63% each received prior (neo)adjuvant treatment. The PD-L1-positive population included 369 patients (185 and 184 patients in the two groups, respectively). Analysis of the co-primary efficacy endpoints (final for PFS, and first interim for OS), completed after 736 PFS events (representing 81.6% of patients) and 389 deaths (43.1%) had occurred in the ITT population (median follow-up of 12.9 months), showed that treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel resulted in a statistically significant reduction in the risk of disease worsening or death in the ITT population (median PFS 7.2 vs. 5.5 months, respectively; hazard ratio [HR]=0.80, 95% CI: 0.69 to 0.92, p=0.0025). In the PD-L1-positive population, median PFS was 7.5 versus 5.0 months in the two groups, respectively; HR=0.62, 95% CI: 0.49 to 0.78, p<0.0001. At this first interim analysis of OS, there was a trend for prolonged OS in the ITT population (median OS 21.3 vs. 17.6 months, respectively; HR=0.84, 95% CI: 0.69 to 1.02, p=0.0840), with a clinically meaningful 9.5-month OS improvement in the PD-L1-positive subpopulation (median OS 25.0 vs. 15.5 months, respectively; HR=0.62, 95% CI: 0.45 to 0.86). Due to the hierarchical statistical design, OS results were not formally tested in the PD-L1-positive subpopulation. In the ITT population, investigator-assessed ORR was 56% in the atezolizumab plus nab-paclitaxel group compared to 46% in the placebo plus nab-paclitaxel group (treatment-difference 10%, p=0.0021). In the PD-L1-positive subpopulation, ORRs were 59% versus 43% in the two groups, respectively (treatment difference 16%, p=0.0016). Median DoR was 7.4 months versus 5.6 months in the two groups, respectively in the ITT population, and 8.5 months versus 5.5 months, respectively in the PD-L1-positive subpopulation (Schmid et al. 2018; WO29522 Primary Clinical Study Report, Report No. 1085705; Roche Data on File).

A pre-planned second interim OS analysis for IMpassion130 was performed based on a CCO date of 2 January 2019, after 534 patients (59.2%) had died in the ITT population (median duration of survival follow-up of 18.0 months). Consistent with the OS results at the first interim analysis, the co-primary endpoint of OS at the second interim analysis was not significant in the ITT population as the pre-specified boundary (HR $\leq$ 0.818, available $\alpha = 0.021$) was not crossed (stratified HR=0.86, 95% CI: 0.72 to 1.02, p−value = 0.0777). Due to the

pre-specified Statistical Analysis Plan (SAP) entailing hierarchical testing for OS first in the ITT and then in the PD-L1–positive population, the difference between the treatment arms for OS in the PD-L1–positive population was not formally tested. However, a clinically meaningful improvement in OS continued to be observed in the PD-L1–positive population, with median OS of 25.0 months versus 18.0 months in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups (stratified HR=0.71, 95% CI: 0.54 to 0.93) (Schmid et al. 2020; WO29522 Update Clinical Study Report, Report No. 1092074; Roche Data on File).

At the final OS analysis, completed after 666 patients (73.8%) had died in the ITT population (median survival follow-up of 18.8 months), median OS was 21.0 months versus 18.7 months in the atezolizumab plus nab-paclitaxel vs placebo plus nab-paclitaxel groups, respectively in the ITT population (stratified OS HR=0.87, 95% CI: 0.75 to 1.02; p-value=0.077), and 25.4 months versus 17.9 months, respectively in the PD-L1 positive population (stratified OS HR=0.67, 95% CI: 0.53 to 0.86; not formally tested due to the prespecified testing hierarchy) (Emens et al. 2020; WO29522 Update Clinical Study Report, Report No. 1100481; Roche Data on File; Emens et al. 2021).

As of the second interim OS analysis, consistent with results of the first interim OS analysis, a statistically significant improvement in investigator-assessed PFS was demonstrated with atezolizumab plus nab-paclitaxel relative to placebo plus nab-paclitaxel in both the ITT population (stratified HR=0.80, 95% CI: 0.69 to 0.92; p–value = 0.0021) and the PD-L1–positive population (stratified HR=0.63, 95% CI: 0.50 to 0.80; p-value $<$ 0.0001). While the PFS analysis was already final at the time of the first interim OS analysis, the updated PFS analysis results presented at the second interim OS analysis confirm the PFS benefit in the PD-L1–positive population and remain consistent, statistically significant, and clinically meaningful (Atezolizumab Investigator's Brochure).

Exploratory efficacy analyses from IMpassion130 indicated that PD-L1 expression on immune cells (ICs) is the most robust predictive biomarker for selecting patients with untreated mTNBC who benefit from atezolizumab plus nab-paclitaxel. Intratumoral CD8 was well correlated with PD-L1-positivity and was consequently predictive of atezolizumab plus nab-paclitaxel efficacy for PFS and OS (*Emens et al. 2021*).

In summary, the Impassion130 study demonstrated that the largest and most consistent improvements in PFS, ORR, and OS for the addition of atezolizumab to nab-paclitaxel occurs in patients with metastatic TNBC whose tumours are PD-L1-positive.

Results of Study MO39196 (IMpassion131)

The combination of atezolizumab and paclitaxel compared to placebo plus paclitaxel is currently being evaluated in a global, randomised, double-blind Phase III study (MO39196/IMpassion 131 study; ClinicalTrials.gov identifier: NCT03125902) in patients with previously untreated unresectable locally advanced or metastatic TNBC. Eligible patients were randomised (N=651) in a 2:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus paclitaxel (90 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. The pre-specified primary efficacy endpoint is investigator-assessed PFS by RECIST v1.1, tested hierarchically first in the PD-L1+ (IC ≥1%) population, then in the ITT population. Of the 651 randomised patients, 292 (45%) had PD-L1+ metastatic TNBC. Primary analyses of PFS were completed after 179 PFS

events (representing 61.3% of patients) and 438 PFS events (67.3% of patients) had occurred in the PD-L1+and ITT populations, respectively. The results showed no significant improvement in the atezozolizumab plus paclitaxel compared to the placebo plus paclitaxel group in either the PD-L1+ subset (median PFS 6.0 vs. 5.7 months, respectively; HR=0.82, 95% CI: 0.60 to 1.12; p=0.20), or in the ITT population (median PFS 5.7 months vs. 5.6 months, respectively). Similarly, analysis of OS (secondary endpoint), completed after 120 (41.1%) and 304 (46.7%) of patients had died in the PD-L1+and ITT populations, respectively, showed no significant survival benefit in either population (Miles et al. 2020; Miles et al. 2021).

1.2.2.4 Safety of Atezolizumab Combined with Chemotherapy

Adverse Events in the mTNBC Subpopulation of Study GP28328

As of 23 April 2018, all 33 (100%) safety-evaluable mTNBC patients experienced at least one adverse event, 28 patients (84.8%) experienced a Grade 3-4 adverse event, no patient experienced a Grade 5 adverse event, 18 patients (54.5%) experienced a serious adverse event, and 3 (9.1%) experienced an adverse event leading to discontinuation of atezolizumab. Refer to the Atezolizumab Investigator's Brochure for details.

Adverse Events in the Overall Population of Study GP28328

As of the data cut-off of 23 April 2018, there were 229 safety-evaluable patients enrolled across six treatment arms in Study GP28328. All 229 (100%) safety-evaluable patients reported at least one adverse event, 175 patients (76.4%) experienced a Grade 3-4 adverse event, 6 patients (2.6%) experienced a Grade 5 adverse event, 122 patients (53.3%) experienced a serious adverse event, and 26 (11.4%) experienced an adverse event leading to discontinuation of atezolizumab. Refer to the Atezolizumab Investigator's Brochure for details.

The safety profile of atezolizumab was generally consistent across treatment arms. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with exacerbation of known adverse events associated with either agent individually. The adverse events observed for atezolizumab in combination with chemotherapy are consistent with the known risks of each study treatment. Available data suggest that atezolizumab can be safely combined with standard chemotherapy treatments and/or bevacizumab.

Refer to the Atezolizumab Investigator's Brochure for further details on clinical studies of atezolizumab.

Adverse Events in Study WO29522 (IMpassion130)

As of the latest CCO date of 14 April 2020, safety data were available for 890 patients with metastatic TNBC in the Safety-evaluable population (460 in the atezolizumab plus nab-paclitaxel group, and 430 patients in the placebo plus nab-paclitaxel group). Adverse events occurred in 99.3% versus 97.9% of patients in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups, respectively, and Grade 3-4 adverse events occurred 50.7% versus 42.6% of patients in the two groups, respectively. Adverse events (all grades) that occurred at a ≥5% higher frequency in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel group included nausea, cough, neutropenia, pyrexia, pruritus, dizziness, hypothyroidism, and stomatitis. The only Grade 3-4 adverse events occurring in ≥5% of patients were neutropenia reported in 8.5% versus 8.1% of patients in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups,

respectively), and peripheral neuropathy (reported in 5.7% vs. 2.8% of patients in the two groups, respectively) (WO29522 Update Clinical Study Report, Report No. 1100481; Roche Data on File).

Serious adverse events occurred in 23.9% versus 18.6% of patients in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups, respectively, and fatal adverse events occurred in 1.3% versus 0.7% of patients in the two groups, respectively. Two of the six fatal adverse events in the atezolizumab plus nab-paclitaxel group (autoimmune hepatitis [considered related to blinded atezolizumab], and septic shock [considered related to nab-paclitaxel], and one of three fatal AEs in the placebo plus nab-paclitaxel group (hepatic failure [considered related to blinded study drug and nab-paclitaxel]) were assessed as treatment-related. One patient in each group experienced a Grade 5 adverse events of special interest (autoimmune hepatitis in the atezolizumab plus nab-paclitaxel group and hepatic failure in the placebo plus nab-paclitaxel group). Grade 3-4 adverse events of special interest occurred in 8.5% and 4.7% of patients in the two groups, respectively. Overall, combination treatment with atezolizumab plus nab-paclitaxel was well tolerated in this study, with a safety profile consistent with that of each agent (WO29522 Update Clinical Study Report, Report No. 1100481; Roche Data on File).

Adverse Events in Study MO39196 (IMpassion131)

Overall, the safety profile was consistent with the known risks of each study drug. Two percent of patients in each group experienced a Grade 5 adverse event. The percentages of patients experiencing Grade 3/4 adverse events were similar among patients treated with atezolizumab and paclitaxel compared to placebo and paclitaxel (49% vs. 43%, respectively) (Miles et al. 2020).

1.2.2.5 Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

Based on available PK data exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered Q3W. Based on a population PK analysis that included 472 patients from Studies PCD4989g and JO28944, in the dose range of 1 mg/kg to 20 mg/kg, the typical population clearance was 0.20 L/day, the volume of distribution at steady state (V_{ss}) was 6.9 L, and the terminal half-life ($t_{1/2}$) was 27 days. The population PK analysis suggested that steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the concentration-time curve (AUC), maximum concentration (C_{max}), and trough concentration (C_{min}) was 1.91, 1.46, and 2.75-fold, respectively, following IV administration of atezolizumab 1200 mg Q3W. Based on an analysis of exposure-safety, and exposure-efficacy data, the following factors had no clinically relevant effect: age (21 to 89 years), body weight, sex, positive ADA status, albumin levels, tumour burden, region or race, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status. The effect of moderate or severe hepatic impairment (bilirubin > upper limit of normal [ULN] and AST > ULN or bilirubin ≥ 1.0 to 1.5 x ULN and any AST elevation) on the PK of atezolizumab is unknown (Atezolizumab Investigator's Brochure).

The development of ADA has been observed in patients at all dose levels. Positive ADA status against atezolizumab led to approximately 13% reduction in overall exposure, with a trend for lower C_{min} values in the ADA positive subgroup in Study PCD4989g. While a subset of ADA-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab

Q3W experienced a reduction of atezolizumab C_{min} to below the PK assay lower limit of quantification (LOQ), patients receiving 10 to 20 mg/kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the LOQ and the target serum concentration of 6 μg/mL (Deng et al. 2016).

In the monotherapy all-patient population, the post-baseline incidence of treatment-emergent atezolizumab ADA (treatment-induced and enhanced) was 37.0% (1002/2705), and the incidence of hypersensitivity events and infusion-related reactions was low and consistent between ADA-positive than ADA -negative patients; refer to the current Atezolizumab Investigator's Brochure for further details.

In the IMpassion130 study, the incidence of treatment-emergent ADAs among patients receiving atezolizumab plus nab-paclitaxel was 13.1% and 11.8% in the ITT and PD−L1-positive populations, respectively. ADA positivity had no clinically relevant effect on PK, although, on average, C_{min} at steady state was approximately 25% lower in ADA-positive vs ADA-negative patients. The overall safety profile was generally concordant between ADA-positive and ADA-negative patients based on the incidence of related adverse events (93.0% vs. 97.9%, respectively), related Grade 3-4 adverse events (40.4% vs. 40.6%, respectively), SAEs (28.1% vs. 21.5%, respectively), adverse events leading to study treatment discontinuation (17.5% vs 15.9%, respectively), and adverse events of special interest (52.6% vs. 58.6%, respectively) (WO29522 Clinical Study Report; Roche Data on File).

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Atezolizumab

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

As detailed in Section 1.1.2.3, PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors: PD-1 and B7.1. PD-L1 is expressed on many cancer and immune cells, and overexpression of PD-L1 on tumour cells has been reported to impede anti-tumour immunity (Blank and Mackensen 2007; Herbst et al. 2014). Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation and secretion of cytotoxic mediators, and restricts tumour cell killing (Herbst et al. 2014). The PD-1/PD-L1 pathway has been implicated in tumours evading immune surveillance. Therefore, interruption of the PD-L1/PD-1 and the PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumour-specific T-cell immunity (Blank and Mackensen 2007; Chen and Mellman, 2013; Herbst et al. 2014; Saha and Nanda, 2016).

The rationale for investigating PD-L1 inhibitors in TNBC stems from a number of key clinical observations. ER-negative breast cancers have a higher density of TILs than their ER-positive counterparts (Loi et al. 2014), and greater numbers of TILs have been associated with better clinical outcomes in patients with TNBC ([No author] 2015). PD-L1 expression is also more prevalent in TNBC than in other breast cancer subtypes (Emens et al. 2015). TNBCs have a higher mutational burden compared with their ER-positive counterparts, and have been

linked with increased immunogenicity (Wang et al. 2014). Gene expression profiling of TNBCs has identified an immunomodulatory subtype that is characterised by increased expression of genes involved in T-cell function (Lehmann et al. 2011; Saha and Nanda, 2016). Due to the higher mutation rate and a higher number of TILs relative to other breast cancer subtypes, TNBC may be particularly susceptible to immunotherapy ([No author] 2015).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies, including patients with TNBC, who have failed standard-of-care therapies. The observation that high CD8+ T-cell density in primary breast tumours is correlated with improved OS, and that mTNBC tumours have fewer TILs than their matched primary tumours, suggests that the immune system is able to partially restrain human breast cancer but that immune suppression becomes more prevalent with increasing growth and metastasis (Cimino-Mathews et al. 2013; Adams et al. 2014; Loi 2014). The identification of immune-enriched subtypes of TNBC underscores the potential to harness pre-existing host anti-tumour immunity in this disease (Lehmann et al. 2011). In this setting, re-invigorating T-cell activity with atezolizumab may be an effective treatment strategy.

Atezolizumab has been generally well tolerated in clinical trials (see Section 1.2.2.2 and Section 1.2.2.4); adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/elevated transaminases, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab (Refer to Atezolizumab Investigator's Brochure for comprehensive and detailed information).

In the setting of the COVID-19 pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acuteSevere Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4).

1.3.2 Chemotherapy and Combination Treatment with Atezolizumab

Preliminary safety data from Study GP28328 indicate that atezolizumab can be safely combined with chemotherapy (several combinations have been evaluated and determined to be well tolerated; refer to the Atezolizumab Investigator's Brochure for details). Specifically, atezolizumab was tested in combination with carboplatin plus nab-paclitaxel or paclitaxel in patients with previously untreated NSCLC and is being tested in combination with neoadjuvant carboplatin and nab-paclitaxel in patients with TNBC. Studies evaluating atezolizumab in combination with gemcitabine and cisplatin in patients with metastatic bladder cancer are also ongoing. No exacerbation of chemotherapy-associated adverse events has been reported to date. There are currently no clinical data pertaining to the concomitant use of atezolizumab and capecitabine; however, this combination treatment is currently evaluated in a Phase II clinical trial in patients with metastatic colorectal cancer (ClinicalTrials.gov identifier: NCT02291289).

Select synergistic anti-cancer combinations have been shown to produce faster and more significant response rates compared with monotherapy in patients with TNBC (Zeichner et al.

2016). Therefore, the current study will evaluate the benefits of adding atezolizumab to one of two chemotherapy regimens in patients with mTNBC.

There is increasing evidence that in addition to causing tumour cell death, certain conventional chemotherapies may have immunogenic effects (Zitvogel et al. 2008). Tumour cell killing by cytotoxic chemotherapy can be expected to expose the immune system to high levels of tumour antigens, and re-invigorating tumour-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signalling may result in deeper and more durable responses compared with standard chemotherapy alone.

A rationale for the choice of chemotherapy as the comparator, including the selected doses of chemotherapy is provided in Section 3.3.3.

In summary, combination treatment with atezolizumab and chemotherapy offers the potential for clinical benefit in patients with mBC.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with inoperable *locally advanced or metastatic* TNBC. Eligible patients should have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. Patients must have experienced disease progression within 12 months (<12 months) from the last treatment with curative intent for early breast cancer (eBC). Specific objectives and corresponding endpoints for the study are outlined in **Table 2** below.

Table 2 Study Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy	• Overall survival (OS), defined as time from randomisation to death from any cause. OS will be tested hierarchically in the following fixed order: o In the population with programmed death-ligand 1 (PD-L1)-positive tumour status, as defined in Section 6; o In the modified intent-to-treat (mITT) population, as defined in Section 6.
Secondary Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy	• 12-month survival rate, defined as the proportion of patients alive 12 months after randomisation • 18-month survival rate, defined as the proportion of patients alive 18 months after randomisation • Progression-free survival (PFS), defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or death from any

Objectives	Corresponding Endpoints
	cause, whichever occurs first. PFS will be tested hierarchically in the following fixed order: o In the PD-L1-positive population, as defined in Section 6; o In the mITT population, as defined in Section 6. • Objective response rate (ORR), defined as the proportion of patients with an objective response, defined as a complete response (CR) or a partial response (PR), as determined by the investigator according to RECIST 1.1. ORR will be tested hierarchically in the following fixed order: o In the PD-L1-positive population, as defined in Section 6; o In the mITT population, as defined in Section 6. • Duration of objective response (DoR), defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST 1.1, or to death from any cause, whichever occurs first • Clinical benefit rate (CBR), defined as the proportion of patients with a CR or a PR or stable disease (SD) that lasts ≥ 6 months, as determined by the investigator according to RECIST 1.1. In addition, confirmed objective response rate (C-ORR) and duration of confirmed response (C-DoR) will be analysed. Details will be provided in the Statistical Analysis Plan (SAP).
• To evaluate patient-reported outcomes (PROs) of global health status (GHS)/quality of life (QoL) associated with atezolizumab plus chemotherapy compared with chemotherapy alone, as measured by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)	• Time to confirmed deterioration (TTD) of GHS/QoL, defined by a minimally important decrease of ≥10 points at two consecutive assessment time-points on the GHS/QoL scale (Items 29, 30) of the EORTC QLQ-C30
Exploratory Efficacy Objectives:	
• To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab plus chemotherapy compared with placebo plus chemotherapy, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23)	• Mean and mean changes from baseline in function (role physical, emotional, social, cognitive) and disease/treatment-related symptoms by treatment cycle, as assessed by the function scales and all symptom items/scales of the EORTC QLQ-C30 and the QLQ-BR23

Objectives	Corresponding Endpoints
• To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to chemotherapy compared with placebo plus chemotherapy, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical wellbeing subscale of the Functional Assessment of Cancer Therapy: General (FACT-G) quality of life instrument	• Proportion of patients reporting each response option at each assessment time point for item GP5 from the FACT-G
• To evaluate health utility as measured by the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire, to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L questionnaire
Specific Efficacy Objectives for Patients Recruited in China:	
• The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus chemotherapy compared with placebo plus chemotherapy as measured by OS and other efficacy endpoints in the China population (enrolled in the Global study and during additional recruitment in China) is consistent with the efficacy observed in the Global population (Global study).	• As described for the Global study
Safety Objectives:	
• To evaluate the safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy	• Incidence, nature, and severity of adverse events (AEs), with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE 4.0) • Change from baseline in targeted vital signs and physical findings • Change from baseline in targeted clinical laboratory test results
Pharmacokinetics Objectives:	
• To characterize the pharmacokinetics (PK) of atezolizumab when administered with carboplatin/gemcitabine or with capecitabine in patients with breast cancer	• Peak and trough of atezolizumab concentrations in serum (Cmax and Cmin) at specified time points during treatment

Objectives	Corresponding Endpoints
Immunogenicity Objective:	
• To evaluate the immunogenicity of atezolizumab	• Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline.
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objectives:	
• To assess the efficacy and safety of atezolizumab plus chemotherapy according to programmed death−ligand 1 (PD-L1) status	• Relationship between PD-L1 protein expression by immunohistochemistry (*VENTANA PD-L1 (SP142) Assay*) in screening tumour tissue and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC1/2/3).
Exploratory Biomarker Objectives:	
• To assess biomarkers that are predictive of response to atezolizumab (i.e., predictive biomarkers), are associated with outcomes independent of treatment (i.e., prognostic biomarkers), as well as pharmacodynamic exploratory biomarkers in tumour tissue (e.g. screening, on-treatment*, and at disease progression sample*) and blood* and their association with disease status and/or response to study drug. • To assess changes in blood-* and tissue-based biomarkers during chemotherapy +/- atezolizumab treatment. • To assess whether immune biomarker findings from this study are consistent with findings in other studies in TNBC or in other tumour types.	• Relationship between tumour immune-related or disease type-related biomarkers (including but not limited to TILs and cluster of differentiation CD8) by immunohistochemistry in tumour tissues, and clinical outcomes. • Relationship between PD-L1 status measured by various immunohistochemistry assays and clinical outcomes. • Relationship between certain molecular subgroups and pre-defined gene signatures by ribonucleic acid (RNA) expression analysis in tumour tissues, and clinical outcomes. • Relationship between deoxyribonucleic acid (DNA) mutations and mutational burden assessed in tumour tissues, and clinical outcomes. • Relationship between exploratory biomarkers (including but not limited to circulating cell-free DNA, proteins, and cytokines) in plasma* collected before treatment, during treatment and at disease progression, and clinical outcomes. • Changes in blood-* and tissue- based biomarkers under chemotherapy +/- atezolizumab treatment in relation to clinical outcome. • Correlation of immune biomarker findings in blood* and tissue samples from this study to findings from other studies in TNBC and other tumour types.

* Plasma, whole blood, and optional tumour samples (on-treatment and at disease progressions) for exploratory biomarker analyses will not be collected from patients enrolled in mainland China. Patients enrolled in mainland China will only contribute to exploratory biomarker analyses that are based on mandatory tumour tissue samples collected at screening. The number of required slides for exploratory analyses using tumor tissue samples are contingent upon the review and approval of the exploratory research by each site's Institutional Review Board/Ethics Committee (IRB/EC), and upon the review and approval by the Human Genetics Resources Administration of China (HGRAC) exploratory application.

All requirements described in this protocol apply to the Global Study, unless otherwise specified; requirements specific to the China population are marked as such throughout the protocol.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of the Study Design

This is a Phase III, global, double-blind, two-arm, placebo-controlled, randomised study designed to evaluate the efficacy and safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with inoperable *locally advanced or metastatic* TNBC. Eligible patients should have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. Patients must have experienced disease progression within 12 months (< 12 months) from the last treatment with curative intent for eBC.

Global Study: A total of approximately 572 patients will be randomised in the study. Following the enrolment of 382 patients with inoperable *locally advanced or metastatic* TNBC (irrespective of PD-L1 tumor status, referred to as 'all-comers'), approximately 190 additional patients with PD-L1-positive tumour status will be randomised, in order to reach approximately 330 patients with PD-L1-positive tumor status required for the primary endpoint analysis of OS in the PD-L1 positive population.

Additional Enrolment in China: After approximately 572 patients have been randomised in the Global study, global recruitment will be closed. Additional patients with PD-L1-positive tumor status may be subsequently randomised in China only, following the same randomisation procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1-positive tumour status in mainland China (including patients from China enrolled in the Global study), referred to as the China population. The schedule of assessments and study treatments for these patients will be identical to those in the Global study, with the following exceptions: patients enrolled in mainland China will not undergo plasma, whole blood, and optional tumour sample collections for exploratory biomarker assessments. Analyses based on the China population will be performed and summarised separately.

The following applies to all patients randomised in the study unless otherwise noted.

Patients who do not meet the criteria for participation in this study (screen failure), may qualify for an additional re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion.

Patients are not required to re-sign the consent form if they are re-screened within 28 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log. See Section 4.5.1.

Results of screening tests within the protocol-defined screening window may be used rather than repeating required tests. For patients who are re-screened, all eligibility criteria must be

re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria.

Patients will be assessed for eligibility during the 28-day screening period prior to enrolment and randomisation; refer to Appendix 1 for details. A screening tumour sample must be tested at the designated central study laboratory to confirm PD-L1 expression and either locally or at the designated central study laboratory to confirm triple-negative tumour status before a patient will be considered eligible for the study. TNBC is defined as human epidermal growth factor 2 (HER2), oestrogen receptor (ER) and progesterone receptor (PR) negative disease determined in accordance with the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (HER2: Wolff et al. 2018; ER and PR: Hammond et al. 2010; Allison et al. 2020). Triple-negative tumour status assessed locally prior to randomisation requires subsequent confirmation (retrospectively) by the designated central laboratory.

A representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen will be tested for PD-L1 expression, as assessed by central laboratory using the *investigational VENTANA PD-L1 (SP142) Assay*. Tumor tissue should be of good quality based on total and viable tumor content and must be prospectively evaluated for PD-L1 expression prior to randomisation. A tumor specimen obtained from relapsed metastatic or locally advanced disease may be submitted, if clinically feasible. If a fresh tumour sample is not clinically feasible, either the primary diagnosis, the surgical resection sample, or the most recent formalin-fixed, paraffin-embedded (FFPE) tumour biopsy should be used.

Eligible patients will be randomised in a 1:1 ratio to receive atezolizumab with chemotherapy (**Arm A**) or placebo with chemotherapy (**Arm B**). For each patient, chemotherapy (carboplatin/gemcitabine or capecitabine) will be selected by the investigator prior to randomisation; however, capecitabine will be mandatory for patients who have received prior platinum therapy for the treatment of their eBC. Overall, and per country/region, approximately 30% of patients randomised in the study should receive capecitabine, and approximately 70% of patients should receive. Randomisation will be stratified by the following three factors: presence of visceral (lung and/or liver) metastases (yes vs. no), tumour PD-L1 status (tumour-infiltrating IC 0 vs. IC1/2/3) and chemotherapy choice (carboplatin/gemcitabine vs. capecitabine). Additional PD-L1 positive patients enrolled under protocol version 4.0 (and beyond) will only be stratified according to the presence of visceral metastases and chemotherapy choice.

Patients should receive their first dose of study treatment no later than 3 calendar days after randomisation. Study treatment will be delivered as follows:

Arm A

Atezolizumab 1200 mg by IV infusion on day 1 of each 3-week treatment cycle with either:

- gemcitabine 1000 mg/m^2, followed by carboplatin target area under the curve (AUC) 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle

or

- capecitabine 1000 mg/m^2 twice daily orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle.

Arm B

Placebo 1200 mg by IV infusion on day 1 of each 3-week treatment cycle with either:

- gemcitabine 1000 mg/m^2, followed by carboplatin target AUC 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle

or

- capecitabine 1000 mg/m^2 twice daily orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle.

Study treatment will continue until disease progression per RECIST 1.1, unacceptable toxicity, or patient or investigator decision to discontinue treatment. Atezolizumab/placebo and chemotherapies may be discontinued for toxicity independently of each other in the absence of disease progression. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Patients who have been randomised will not be replaced.

Tumour assessments will be performed every 8 weeks (± 1 week) for the first 12 months after treatment initiation and every 12 weeks (± 1 week) thereafter until disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Tumour assessments will be performed according to the specified schedule regardless of dose delays, interruptions, or discontinuations. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumour assessments according to the protocol-specified schedule until they experience disease progression, withdraw consent, or die, or until the study closes, whichever occurs first, even if they started another anti-cancer therapy after study treatment discontinuation.

For estimation of PFS, ORR, and DoR, tumour response will be based on RECIST v1.1. Imaging data used for tumour assessment may be retrospectively collected by the Sponsor to enable centralised, independent review of response endpoints by an Independent Review Committee in the future, if necessary.

Cross-over between treatment arms will not be allowed.

Given that the primary efficacy endpoint of the study is OS, every effort should be made to avoid unblinding and continue survival data collection as per protocol. Treatment codes should not be broken except in emergency situations or in cases of disease progression, where knowledge of study treatment assignment will affect later-line treatment of the patient, as defined in Section 4.2.3.2. The Investigator must obtain Sponsor approval for the potential unblinding. Survival data and post-study treatment cancer treatment information must continue to be collected for unblinded patients.

Safety assessments will include regular evaluation of adverse events and conduct of physical examinations, vital signs, clinical laboratory tests (haematology, blood chemistry, urinalysis) and electrocardiograms (ECGs). Adverse events will be graded according to the NCI CTCAE v4.0.

PK and atezolizumab immunogenicity analyses will be based on blood samples collected before, during and after study treatment. A detailed schedule of sample collections for PK and immunogenicity analyses is included in Appendix 2.

Blood and tumour samples will be collected in order to conduct exploratory biomarker assessments investigating mechanisms of study treatment activity within the tumour microenvironment, possible resistance mechanisms, and potential predictive and prognostic indicators.

As described above, all patients enrolled in the Global study and all patients in the China population will undergo mandatory tumour sample collection at screening. The mandatory tumour sample submitted prior to enrolment for ER/PR, HER2 and PD-L1 testing will be included in the exploratory biomarker evaluations. The schedule of sample collections for biomarker research is included in Appendix 2. Acceptable tumour samples for biomarker analyses are core needle biopsies for deep tumour tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine needle aspirates, brushings, cell pellets from pleural effusions, samples from bone metastases, and lavage samples are not acceptable.

In addition, for patients enrolled in the Global study (except for patients enrolled in mainland China):

- Plasma samples will be collected at baseline, during treatment and at disease progression.
- A whole blood sample will be collected at baseline for germline mutation analyses.
- If deemed clinically feasible by the investigator, optional tumour samples for biomarker analyses will be collected pre-treatment on Day 1, Cycle 2 and at disease progression, provided that the patient consented to this optional procedure.

  Plasma, whole blood, and optional tumour samples for biomarker analyses will not be collected from patients enrolled in mainland China.

The schedule of sample collections for biomarker research is included in Appendix 2.

Patients will undergo a treatment discontinuation visit 30 days after their last study treatment and will immediately enter post-treatment follow-up. Patients will be followed for disease progression (if progression has not yet occurred) and survival every 3 months for at least 18 months from randomisation unless death, withdrawal of consent, loss to follow-up, or study

termination by the Sponsor occurs sooner. Anti-cancer treatments received during this follow-up period will be documented.

A schedule of activities is provided in Appendix 1. A study design schema is presented in **Figure 1**.

3.1.2 Study Committees

A Steering Committee (SC) will provide scientific oversight of the trial. Details of the composition and mandate of the SC will be provided in the SC Charter.

An independent Data Monitoring Committee (iDMC) will be in place for periodic review of aggregate safety data during the study and an interim efficacy analysis, should the latter occur. Members of the iDMC will be independent of the Sponsor and will follow a charter that outlines their roles and responsibilities. The iDMC will meet approximately every 6 months from the point of first patient in (FPI) until the last patient has completed study treatment, to review study conduct and unblinded safety data prepared by an independent Data Coordinating Centre (iDCC). The safety data will include demographic, adverse event, serious adverse event, adverse events leading to treatment discontinuations and relevant laboratory data.

Following each data review, the iDMC will provide recommendations to the Sponsor as to whether the study should continue as planned, or be amended, or whether the study should be stopped on safety grounds (i.e., evidence of harm). The Sponsor's Data Review Board (DRB; a group consisting of employees of the Sponsor empowered to make critical decisions) will make a decision based on the iDMC's recommendations. The final decision will rest with the Sponsor.

Any outcomes of the iDMC safety reviews that affect the study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Board/Ethics Committee (IRB/EC).

Further details on the composition and responsibilities of the iDMC and the safety review plan will be provided in the iDMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is definedas the last patient last visit (LPLV) (regardless of *whether* the *last patient last visit is for a patient who is part of the Global study or the China population)*.
Global Study

Total study recruitment (of all-comers and additional patients with PD-L1-positive tumour status) is expected to occur over approximately 53 months.

This is an event driven trial. The CCO date for the final OS analysis will be confirmed when the targeted number of mortality events (247 deaths) have occurred in the PD-L1-positive population, which is expected approximately 58 months after the first patient was randomised ("first patient in"; FPI) in the study.

The actual length of the study and the time for final analysis will depend on the actual recruitment rate and the number of events that occur. Mortality events will be monitored throughout the course of the study, and study timelines might be updated.

In addition, the Sponsor may decide to terminate the study at any time (see Section 4.6.3). If the Sponsor decides to terminate the study, patients who are still receiving study treatment may be eligible for continued (post-trial) access to atezolizumab as described in Section 4.3.5.

3.2.1 China Population

The OS analysis for the China population will be conducted when approximately 49 deaths in the China population have been observed. The CCO date of OS analysis in the China population may be revisited according to the data maturity and estimated treatment effect from the global population.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for the Atezolizumab Dose and Schedule

Atezolizumab will be administered at a dose of 1200 mg via IV infusion on Day 1 of each 3-week treatment cycle (Q3W), aligned with the chemotherapy schedule. The fixed dose of 1200 mg Q3W (weight-based equivalent of 15 mg/kg) has been approved for treating patients with urothelial carcinoma, NSCLC, SCLC, and hepatocellular carcinoma, as outlined in the prescribing information.

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 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 (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.3.2 Rationale for Patient Population and Analysis Groups

The target population will include patients with inoperable *locally advanced or metastatic* TNBC. Eligible patients should have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. Patients must have progressed within 12 months (<12 months) from the last treatment with curative intent for their eBC. Given the rapid relapse, this population is considered to have a more aggressive form of advanced TNBC, for which there are currently no standard of care options. Furthermore, these patients are typically excluded from clinical trials of anti-cancer agents. These considerations underscore the high unmet medical need in the inoperable *locally advanced or metastatic* TNBC setting.

As detailed in Section 1.1.1, TNBC is more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with metastatic TNBC are characterised by a more aggressive course compared to other subtypes (Wahba and El-Hadaad 2015) and a poor clinical outcome (Mersin et al. 2008; Trivers et al. 2009), including worse breast cancer-specific survival and OS (Lin et al 2012), generally with rapid progression and a median OS generally between 13 months (Kassam et al. 2009) and 17.5 months in patients treated with various chemotherapy agents (Roche data on file).

Median OS was shown to be longer for patients with de novo versus relapsed metastatic disease (11 vs. 8 months; p = 0.02) (den Brok et al. 2017).

Although TNBC may respond to chemotherapy, there are no targeted therapies with widespread global approval available for patients with this subtype of breast cancer, and relatively few new agents have been approved for mTNBC (Carey et al. 2012; O'Shaughnessy et al. 2014; Hirshfield and Ganesan, 2014; Zeichner et al. 2016). Therefore, there is a pressing need for clinically active targeted therapy for mTNBC.

Regarding its immunologic properties, TNBC is characterised by high DNA mutational rates (TCGAN, 2012) which have been postulated as a source of immunogenic tumour-specific neoantigens. Consistent with this, a significant proportion of patients with TNBC display CD8+ tumour infiltrating lymphocytes at diagnosis, which has been correlated with a better prognosis (Ali et al. 2014) and suggests that activation of the immune system in patients with TNBC could be utilised to modify the course of the disease.

Atezolizumab showed promising anti-tumour activity, as determined by RECIST v1.1 response, across multiple advanced tumour types (including TNBC) both as monotherapy (Phase Ia Study PCD4989g) as well as in combination with bevacizumab and/or chemotherapy (Phase Ib Study GP28328). In patients with mTNBC, atezolizumab has shown activity as monotherapy (Schmid et al. 2017), and in combination with nab-paclitaxel (Adams et al. 2016).

The rationale for performing the primary analysis of OS in patients with PD-L1-positive tumour status is based on the available results from the global, randomised, double-blind, Phase III IMpassion130 study. Specifically, the significant PFS and OS benefits in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups in the PD-L1-positive subpopulation have identified PD-L1-positive tumour status as a predictive biomarker and subgroup of TNBC patients with enhanced treatment effect (Schmid et al. 2018; *Emens et al. 2021*; Schmid et al. 2020); refer to Section 1.2.2.3 for details. Of note, results of the IMpassion130 study do not indicate a detrimental effect of atezolizumab plus nab-paclitaxel in patients with PD-L1-negative tumour status.

Driven by the results of the two interim analyses of OS in the IMpassion130 study, in protocol version 4.0, the Sponsor amended the primary analysis of the MO39193 (IMpassion132) study to OS in the PD-L1-positive population (analysed first), with OS in the mITT population to be tested hiererachically, only if the previously tested null hypothesis (OS in the PD-L1-positive population) has been rejected. However, formal evaluation of the survival benefit of atezolizumab plus chemotherapy in patients with inoperable *locally advanced or metastatic* PD-L1-positive TNBC requires 247 events with a target sample size of approximately 330 patients with PD-L1-positive tumour status. Based on the 382 'all-comers' enrolled in the Global study, approximately 37% (N=140) of 'all-comer' patients have PD-L1-positive tumour status. Therefore, to avoid the need for a new clinical trial, and to ensure that subsequent exposure to study treatment is limited to patients with an anticipated enhanced treatment effect (as observed in IMpassion130), approximately 190 additional patients with PD-L1-positive tumour status will be randomised in the study. Hence the total sample size will be increased from 382 to approximately 572 patients, allowing for the study to be powered for the analysis of OS in the PD-L1-positive population with approximately 330 patients and 247 required events.

Stratified analyses of the primary endpoint will be completed according to predefined and clinically important randomisation stratification factors, including the presence of visceral (lung and/or liver) metastases (yes vs. no), tumour PD-L1 status (tumour-infiltrating IC0 vs. IC1/2/3) and chemotherapy choice (carboplatin/gemcitabine vs. capecitabine). PD-L1 positive patients enrolled under protocol version 4.0 will only be stratified according to the presence of visceral metastases and chemotherapy choice. Analysis of the relationship between PD-L1 protein expression by IHC in screening tumour tissues and clinical outcomes is a predefined biomarker objective of the study.

3.3.3 Rationale for Concomitant Chemotherapy, including Dosing Regimens

Despite the expansion of the therapeutic landscape for mBC over the last three decades, including the increasing availability of targeted therapies for various BC subtypes, cytotoxic regimens remain standard of care in first-line therapy for patients with mBC, including TNBC (Cardoso et al. 2012; Greene and Hennessy 2015; Hernandez-Aya and Ma 2016; Fukada et al. 2016).

The rationale for including platinum agents in the treatment of TNBC is based on a growing body of preclinical and clinical observations of platinum-conferred sensitivity linked with impaired homologous recombination repair mechanisms present in TNBC and mutations in the BRCA susceptibility gene (Tommiska et al. 2008; Tassone et al. 2009; Gucalp and Traina, 2011; O'Shaughnessy et al. 2011; Isakoff et al. 2015; Yardley et al. 2015).

As detailed in Section 1.1.2.1, the efficacy of platinum agents in metastatic breast cancer is well established (Petrelli et al. 2016). In addition, the clinical activity of platinum therapy in patients with metastatic TNBC has been demonstrated both as single agent (Tutt et al. 2014; Isakoff et al. 2015) or in combination with other anticancer agents (O'Shaughnessy et al. 2011; O'Shaughnessy et al. 2014; Yardley et al. 2015; Michalaki et al. 2016), particularly in TNBC patients with BRCA1/2 mutations (Tutt et al. 2014). Specifically, several randomised trials demonstrated clinical benefits with the combination regimen selected for the current study (gemcitabine 1000 mg/m^2 IV plus carboplatin IV dosed at AUC2 on days 1 and 8 of every 3-week cycle) in metastatic TNBC (O'Shaughnessy et al. 2011; O'Shaughnessy et al. 2014; Yardley et al. 2015), with median PFS and OS of 4.1 to 6 months and 11.1 to 12.6 months, respectively (O'Shaughnessy et al. 2014; Yardley et al.2016).

Accordingly, current ESO/ESMO and National Comprehensive Cancer Network (NCCN) consensus guidelines recommend that a platinum regimen be considered for patients with advanced BRCA-associated TNBC or endocrine-resistant metastatic breast cancer previously treated with an anthracycline and a taxane in the adjuvant or metastatic setting (Cardoso et al. 2014; NCCN Breast Cancer Guideline v2, 2017).

Capecitabine is an effective and established treatment choice for metastatic breast cancer patients who progressed after pre-treatment with anthracyclines and/or taxanes (Li et al. 2015). As detailed in Section 1.1.2.2, several prospective clinical trials showed clinical activity with capecitabine-containing regimens in advanced TNBC, including in combination with ixabepilone (Pivot et al. 2009), doxorubicin and cyclophosphamide (Skrypnikova et al. 2011), cyclophosphamide (Yoshimoto et al. 2012), bevacizumab (Robert et al. 2011; Brufsky et al. 2012), docetaxel (Fan et al.2013; Liao et al, 2013), or cisplatin (Li et al. 2015). In addition, maintenance therapy with capecitabine (after achieving initial disease control with

capecitabine plus docetaxel) was shown to significantly prolong median PFS time in patients with metastatic TNBC (Liang et al. 2014). The capecitabine dose selected for the current study (3-week cycles consisting of capecitabine 1000 mg/m^2 administered orally twice daily [morning and evening] for 2 weeks, followed by a 1-week rest period) was evaluated in large Phase III clinical trials (RIBBON-1, RIBBON-2) in HER2-negative, locally recurrent or metastatic BC (Robert et al. 2011; Brufsky et al.2011), and is one of the dosing schedules recommended in clinical guidelines for the treatment of recurrent or metastatic BC (NCCN Breast Cancer Guideline v2 2017). Furthermore, several randomised studies and retrospective analyses have shown that, in patients who received capecitabine (either as mono- or combination therapy), dose modification of capecitabine is effective in the management of adverse events without compromising efficacy (Leonard et al. 2011).

In summary, both carboplatin/gemcitabine combination and capecitabine are considered suitable treatment options as chemotherapy partners in the current study.

3.3.4 Rationale for Placebo Control

Randomised, double-blind, placebo-controlled trials are the "gold standard" of assessing the effectiveness of a new therapeutic drug. The use of placebo control in cancer clinical trials is scientifically feasible; however, it is ethically justifiable only in certain circumstances, such as in trials with an "add-on" design, in which patients randomly assigned to one arm receive standard therapy plus the investigational drug, while those in the control arm receive standard therapy plus a placebo.

Placebo for atezolizumab will be utilised in this study in combination with chemotherapy in order to minimize potential assessment or observer bias. The use of placebo will allow for a more impartial assessment of overlapping toxicity and the true safety impact of the addition of atezolizumab to chemotherapy. In addition, placebo control can aid in the interpretation of the treatment comparison of PFS, which is a secondary endpoint in this study.

Use of a placebo control under double-blind conditions can also help minimize up-front patient dropout that can occur in an open-label study following randomisation to the control arm. In addition, use of a placebo control may minimize the premature initiation of subsequent therapies or crossover which may otherwise occur when study treatment is not blinded, which makes interpretation of the OS endpoint challenging.

Patients who are randomised to atezolizumab placebo will not be deprived of active therapy because they will receive an active chemotherapy regimen.

Placebo-controlled trials may be necessary or desirable to meet regulatory standards for drug approval. Trials that used standard therapy as background treatment led to recent regulatory approval of several targeted agents in various advanced cancer types (Cohen et al. 2005; Summers et al. 2010; Larkins et al. 2015).

3.3.5 Rationale for Biomarker Assessments

TNBC is a heterogeneous disease and the need for identification and characterization of molecular biomarkers to predict response to therapy, in order to further improve treatment strategies including targeted therapies, is well recognised (Verma et al, 2011; Wahba and El-Hadaad 2015).

PD-L1 expression in triple-negative tumours has been shown to correlate with response to anti-PD-1 therapy (Herbst et al. 2014). This correlation was also observed with atezolizumab in the Phase Ia Study PCD4989g, most notably in urothelial and renal cancers and NSCLC (see Section 1.2.2.1), as well as in Study WO29522 (IMpassion130), in patients with locally advanced or metastatic TNBC (see Section 1.2.2.3). Biomarker samples collected prior to dosing, on-treatment and at disease progression will be assessed in an effort to further understand cancer immunotherapy in TNBC and to identify which patients are most likely to respond to atezolizumab. *Based on results from Study WO29522,* the *VENTANA PD-L1 (SP142) Assay* for the assessment of the PD-L1 protein in tumor cells and tumor-infiltrating immune cells in the FFPE tissues received indication-specific companion diagnostics approval for the use of atezolizumab in TNBC *in the E.U.* Rationale for Mandatory Pre-treatment Tumour Samples

To evaluate the potential predictive significance of PD-L1 expression in mTNBC, representative tumour specimens obtained from metastatic or locally advanced TNBC will be collected prior to randomisation. If a *fresh tumor sample* is not available and a tumour biopsy is not clinically feasible, the primary surgical resection sample or the most recent FFPE tumour biopsy sample may be used. These tumour specimens will also be used for retrospective confirmation of HER2, ER, and PR expression by a designated central testing laboratory in cases were initial prospective confirmation of triple-negative tumour status occurred locally. If multiple tumour specimens are submitted, at least one specimen must be evaluable for PD-L1, to assess tumour PD-L1 expression as determined by IHC. Patients enrolled under protocol version 4.0 (and beyond) must have PD-L1-positive tumour status *(with positivity defined as ≥1% of the tumor area occupied by PD-L1- expressing tumor-infiltrating immune cells of any intensity)* confirmed centrally using the *investigational VENTANA PD-L1 (SP142) Assay* prior to randomisation.

In addition to the assessment of PD-L1 status, other exploratory markers such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab plus chemotherapy, tumour immunobiology, mechanisms of resistance, or tumour type, may also be analysed.

3.3.5.1 Rationale for Optional On-treatment Biopsy Specimen Collection

One optional on-treatment tumour sample will be collected pre-dose on Cycle 2, Day 1 (prior to steroid medication), from patients who have provided consent for paired biopsies. The samples will be analysed for molecular changes occurring after treatment with chemotherapy plus atezolizumab compared to chemotherapy plus placebo. These analyses will help elucidate changes in the immune tumour microenvironment under treatment and early mechanisms of action and resistance to study treatment. The conclusions obtained from these studies will aid in the development of therapies to improve anti-tumour immune response in patients with TNBC.

3.3.5.2 Rationale for Optional Biopsy Specimen Collection at the Time of Radiographic Progression

To test the mechanisms of resistance to the drug combination, consenting patients will undergo a tumour biopsy collection (optional sample; collected if clinically feasible, preferably from new or progressing lesions) at first evidence of radiographic disease progression per

RECIST v1.1. Analysis of biological material (including but not restricted to DNA and RNA sequencing) from these specimens will help elucidate molecular changes associated with resistance to or disease progression after treatment with chemotherapy plus atezolizumab or chemotherapy plus placebo in patients with TNBC.

3.3.5.3 Rationale for Mandatory Blood Sampling for Biomarkers

Changes in different blood biomarkers may provide evidence for biologic activity of atezolizumab in combination with chemotherapy in humans and may allow for the development of a blood-based biomarker to help predict which patients may benefit from atezolizumab plus chemotherapy. An exploratory objective of this study is to evaluate changes in surrogate biomarkers in blood samples.

In addition, potential correlations of these pharmacodynamic markers with the safety and anti-tumour activity of atezolizumab will be explored.

4. MATERIALS AND METHODS

4.1 PATIENTS

The Global study will enrol a total of approximately 572 patients with inoperable *locally advanced or metastatic* TNBC. Eligible patients should have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. Patients must have experienced disease progression within 12 months (<12 months) from the last treatment with curative intent for eBC.

A total of approximately 70 patients with PD-L1-positive tumour status will be enrolled in mainland China (including patients from China enrolled in the Global study). The enrolment criteria will be identical for all patients (global and additional enrolment in China), with the exception of provisions related to prior Chinese traditional medicines for the treatment of cancer, as described below.

4.1.1 Inclusion Criteria

Patients must meet all the following criteria for study entry:

1. Have provided written informed consent
2. Male or female ≥ 18 years of age
3. In the investigator's judgment is willing and able to comply with the study protocol including completion of patient-reported outcomes questionnaires
4. Histologically confirmed TNBC that is either locally recurrent inoperable and cannot be treated with curative intent or is metastatic

   Triple-negative breast cancer, defined as the absence of HER2 overexpression, ER expression and PR expression, must be determined by either local or central testing of a screening tumour sample as defined by ASCO/CAP guidelines (HER2: Wolff et al. 2018; ER and PR: Hammond et al. 2010; Allison et al. 2020). See sample related inclusion criterion below.

5. Prior treatment (of early breast cancer) with an anthracycline and taxane

6. Documented disease progression (e.g., with biopsy sample, pathology, or imaging report) occurring within 12 months (<12 months) from the last treatment with curative intent, i.e.
   - date of the last chemotherapy administration, that included a taxane and anthracycline (neoadjuvant or adjuvant) or
   - date of the primary breast tumour surgery after neoadjuvant treatment whichever occurred last. Adjuvant radiation therapy not considered treatment with curative intent for purpose of calculating <12 months interval requirement.
7. Have not received prior chemotherapy or targeted systemic therapy for their locally advanced inoperable or metastatic recurrence.

   Prior radiation therapy for recurrent disease is permitted. There is no required minimum washout period for radiation therapy; however, patients should have recovered from the effects of radiation before randomisation. Candidate lesions for palliative radiotherapy must be decided prior to study entry.

   China population only: Chinese traditional medicines with an approved indication for cancer treatment are permitted as long as the last administration occurred at least 2 weeks prior to randomisation.
8. Measurable or non-measurable disease, as defined by RECIST 1.1 (Note: previously irradiated lesions may be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation).
9. Availability of a representative formalin-fixed paraffin-embedded (FFPE) tumour block (preferred) or at least 17 unstained slides obtained from relapsed metastatic or locally advanced diseases may be submitted, if clinically feasible, with an associated pathology report, if available. If a fresh tumour sample is not clinically feasible, either the diagnosis sample, the primary surgical resection sample, or the most recent FFPE tumour biopsy sample should be used.
   a. The tumour tissue should be of good quality based on total and viable tumour content and must be evaluated centrally for PD-L1 expression, as determined using *investigational VENTANA PD-L1 (SP142) Assay* prior to enrolment, with positivity defined as $\geq$ 1%, of the tumor area occupied by PD-L1- expressing tumor-infiltrating immune cells of any intensity, and either locally or centrally for HER2, ER, and PR expression prior to enrolment. Patients whose tumour tissue is not evaluable for prospective central testing are not eligible.
   b. If multiple tumour specimens are submitted, patients may be eligible if at least one specimen is evaluable and positive for PD-L1 expression (regardless of whether the tissue is from an archival specimen or freshly collected relapsed disease).

      Acceptable samples include core needle biopsies for deep tumour tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

      Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

      Tumour tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

10. Eastern Cooperative Oncology Group performance status 0-1.
11. Life expectancy ≥ 12 weeks.
12. Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment administration (Cycle 1, Day 1):
    c. ANC ≥ 1500 cells/μL (without granulocyte colony stimulating factor [G-CSF] support within 2 weeks prior to the first study treatment administration). G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1.
    d. Lymphocyte count ≥ 500/μL
    e. Platelet count ≥ 100,000/μL (patients may be transfused to meet this criterion. Following transfusion, a 14-day period is required before Cycle 1, Day 1)
    f. Haemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion. Following transfusion, a 14-day period is required before Cycle 1, Day 1)
    g. AST, ALT, and alkaline phosphatase ≤ 2.5 x the ULN, with the following exceptions:

        Patients with documented liver metastases: AST and ALT ≤ 5× ULN

        Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5× ULN
    h. Serum bilirubin ≤ 1.5× ULN

        Patients with known Gilbert's disease who have serum bilirubin level ≤ 3× ULN may be enrolled.
    i. Patients who are not receiving therapeutic anticoagulation: NR and aPTT ≤ 1.5× ULN. Patients who are receiving an anticoagulant medicinal product must be on a stable anticoagulant regimen and have an INR which is not above the target therapeutic range during the 14 days preceding initiation of study treatment.
    j. Calculated creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault formula).
13. Negative HIV test at screening.
14. Negative hepatitis B surface antigen (HBsAg) test at screening.
15. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening.

    The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive HBcAb test.
16. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening.

    The HCV RNA test will be performed only for patients who have positive HCV antibody test.
17. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraception as defined below:

    Women must remain abstinent or use contraceptive methods with a failure rate of ≤1% per year during the treatment period with any study treatment and for 5 months after the final dose of atezolizumab or 6 months after the last dose of capecitabine,

whichever is later. Women must refrain from donating eggs during the same time period.

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of ≤ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

18. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom and agreement to refrain from donating sperm, as defined below:

    With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of capecitabine or 6 months after the last dose of carboplatin/gemcitabine, whichever is later, to avoid exposing the embryo. Men must refrain from donating sperm during this same period. Due to the possibility of irreversible infertility with carboplatin/gemcitabine, men receiving these chemotherapies should consult with their doctor regarding conservation of sperm prior to treatment initiation.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.For patients enrolled after the recruitment of all-comers is complete:

19. PD-L1-positive tumour status (assessed centrally prior to randomisation), defined as PD-L1 expression on tumour-infiltrating immune cells (IC) of 1% or greater (IC1/2/3).

4.1.2 Exclusion Criteria

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

1. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomisation
2. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.

   Patients with a history of treated CNS lesions are eligible, provided that all of the following criteria are met:

   a. Measurable or non-measurable disease, per RECIST v. 1.1, must be present outside the CNS
   b. No history of intracranial haemorrhage or spinal cord haemorrhage
   c. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
   d. There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
   e. The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 days prior to initiation of study treatment.
   f. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

      Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

3. Symptomatic or rapid visceral progression
4. History of leptomeningeal disease
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) (patients with indwelling catheters such as PleurX® are allowed)
6. Uncontrolled tumour-related pain

   Patients requiring pain medication must be on a stable regimen at study entry.

   Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomisation. Patients should be recovered from the effects of radiation prior to study entry. There is no required minimum recovery period.

   Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to randomisation.

7. Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionised calcium or total calcium > 3 mmol/L or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

8. Malignancies other than TNBC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%) and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)
9. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to randomisation, unstable arrhythmias, or unstable angina

    Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimised in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

10. Presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second or third-degree heart block, evidence of prior myocardial infarction, or QT interval corrected using Fridericia's formula (QTcF) > 470 ms demonstrated by at least two consecutive ECGs
11. Severe infection requiring oral or IV antibiotics within 4 weeks prior to randomisation, including but not limited to hospitalization for complications of infection, bacteraemia, or severe pneumonia.

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

12. Current treatment with anti-viral therapy for HBV.
13. Major surgical procedure within 4 weeks prior to randomisation or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis

    Placement of central venous access catheter(s) (e.g. port or similar) is not considered a major surgical procedure and is therefore permitted.

14. Treatment with investigational therapy within 28 days prior to randomisation
15. Pregnant or lactating or intending to become pregnant during or within 5 months after the last dose of atezolizumab, or within 6 months after the last dose of capecitabine, whichever is later.
16. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.

<u>Exclusion Criteria Related to Atezolizumab</u>

17. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins

18. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the atezolizumab formulation
19. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (refer to Appendix 5)

    Patients with the following are eligible:

    a. history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone
    b. controlled Type 1 diabetes mellitus on a stable insulin dosing regimen
    c. eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
        - rash must cover less than 10% of body surface area
        - disease is well controlled prior to randomisation and only requires low potency topical steroids
        - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral steroids).
20. Prior allogeneic stem cell or solid organ transplantation
21. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computerised tomography (CT) scan

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
22. Active tuberculosis
23. Receipt of a live, attenuated vaccine within 4 weeks prior to randomisation or anticipation that a live, attenuated vaccine will be required during atezolizumab/placebo treatment or within 5 months after the last dose of atezolizumab/placebo
24. Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway targeting agents
25. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to randomisation
26. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, mycophenolate, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, or anticipated requirement for systemic immunosuppressive medications during the trial, with the following exceptions:

Patients who have received acute, low dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

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

27. Poor peripheral venous access
28. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, safety of participation, or interpretation of results. This includes significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome) or any other serious medical condition or abnormality in clinical laboratory tests that meet these criteria in the investigator's opinion.

Exclusion Criteria Related to Capecitabine

29. Inability to swallow pills
30. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis
31. Known dihydropyrimidine dehydrogenase (DPD) deficiency or history of severe and unexpected reactions to fluoropyrimidine therapy in patients selected to receive capecitabine
32. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine in patients selected to receive capecitabine. Use of these drugs is not allowed within 4 weeks of initiation of study treatment that includes capecitabine.
33. Hypersensitivity to any component of capecitabine drug formulation in patients selected to receive capecitabine.

Exclusion Criteria Related to Carboplatin/Gemcitabine

34. Hypersensitivity to platinum containing compounds or any component of carboplatin or gemcitabine drug formulations in patients selected to receive carboplatin and gemcitabine.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Randomisation

This is a randomised, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Eligible patients will be randomised in a 1:1 ratio to receive chemotherapy (carboplatin/gemcitabine or capecitabine) with either atezolizumab (**Arm A**) or placebo (**Arm B**). For each patient, chemotherapy (carboplatin/gemcitabine or capecitabine) will be selected by the investigator prior to randomisation; however, capecitabine is mandatory for patients who have received prior platinum therapy.

The randomisation scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm, and within the following baseline stratification factors:

- Presence of visceral (lung and/or liver) metastases (yes vs. no);
- Tumour PD-L1 status (IC0 vs. IC1/2/3); and
- Chemotherapy choice (carboplatin/gemcitabine vs. capecitabine).

PD-L1 positive patients enrolled under protocol version 4.0 (and beyond) will only be stratified according to the presence of visceral metastases and chemotherapy choice.

The China population will be randomised using the same randomisation method, ratio (1:1), and stratification factors, as described for the Global study patients.

Approximately 30% of randomised patients should receive capecitabine, and approximately 70% of patients should receive carboplatin/gemcitabine overall and per country/region. Patients who have been randomised will not be replaced.

4.2.2 Blinding

Study site personnel, including the investigator, and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment prior to unblinding of the treatment assignment at the study level (refer to Section 4.2.3), with the exception of individuals who require access to patient treatment assignments to fulfil their job roles during a clinical trial. These roles include the IxRS service provider (the external independent statistical coordinating centre responsible for verifying patient randomisation and study treatment kit assignments), PK/pharmacodynamic testing laboratory personnel, and the iDMC members.

Personnel responsible for performing PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate PK and ADA samples to be analysed and assist with cleaning of PK and ADA data. While PK and ADA samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of data collected in this trial. Samples from patients assigned to the comparator arm will not be analysed except by request (e.g., to evaluate a possible error in dosing).

4.2.3 Unblinding

All occurrences of unblinding, including their date, time, and rationale, should be documented in the study file.

Treatment codes should not be broken except in emergency situations or in cases of disease progression, where knowledge of study treatment assignment will affect later-line treatment of the patient or enrolment in a subsequent clinical trial; refer to the circumstances described in Section 4.2.3.2 below. Survival data and post-study treatment cancer treatment information must continue to be collected for unblinded patients.

4.2.3.1 Emergency Unblinding

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected study drug-related toxicity (see Section

5.7) that are considered by the investigator or Sponsor to be related to study drug. In these instances, the patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfil their roles (as defined above), will remain blinded to treatment assignment.

Emergency unblinding by the investigator should be performed only in cases when knowledge of treatment assignment will affect the immediate management of a patient. If unblinding is necessary (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code solely for the patient experiencing the treatment emergent adverse event by contacting the IxRS, and by using a personal identification (PIN) code which is issued to them at the start of the study. Investigators should inform the Medical Monitor that the treatment code has been broken.

Unblinding should not result in the withdrawal of the patients from the study. Every effort should be made to retain unblinded patients and continue data collection as per protocol.

4.2.3.2 Unblinding upon Disease Progression

Given that the primary efficacy endpoint of the study is OS, every effort should be made to avoid unblinding and continue survival data collection as per protocol. Prior to disease progression, the patient's treatment allocation must remain blinded.

Upon radiographic disease progression per RECIST v1.1, and the resulting discontinuation of study treatment, the study drug assignment may be unblinded (for the patient with confirmed disease progression only), provided that the following conditions are met:

- There is an imminent plan to treat the patient with next line of approved treatment or enrolling her/him in a subsequent clinical trial; and
- There is documented evidence provided to the Sponsor that the patient meets the criteria for the next-line of approved treatment or clinical trial, except for invasive/radiation-requiring procedures; and
- The knowledge of treatment allocation (atezolizumab/placebo) in the current study is required to confirm that the patient meets the criteria for the next-line approved treatment or clinical trial; and
- Data entry related to the documented progression is entered in the eCRF; and
- The Investigator obtains Sponsor approval for the potential unblinding.

The study centre will be required to send all requests for unblinding, including documentation of radiographic disease progression, to the Sponsor for approval. Upon Sponsor approval, the IxRS system will provide the site with the study treatment assignment. The Sponsor will not be informed of the patient's treatment allocation at the time of unblinding.

Continued treatment with atezolizumab, beyond radiographic evidence of disease progression per RECIST v1.1, in patients allocated to atezolizumab is not allowed.

4.2.3.3 Unblinding at the Study Level

Treatment assignment will be unblinded *for all randomized patients* at the time of the primary endpoint analysis, after all data have been cleaned and verified and the database has been locked.

To preserve the integrity of China population analysis, unblinding at the study level does not apply to patients in China who are randomized after the CCO date for primary endpoint analysis. The unblinding for those patients will occur at the time of the OS analysis for the China population as described in Section 3.2.1.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

Atezolizumab, placebo, carboplatin, gemcitabine and capecitabine are investigational medicinal products (IMPs) in this study. All IMPs will be provided by the study sponsor. Patients should receive their first dose of study treatment no later than 3 calendar days after randomisation.

Non-investigational medicinal products (NIMPs) used in the study include premedication (see Section 4.4.1.1), medications that may be administered to manage adverse events (see Section 5.1.4), and other permitted concomitant medications (see Section 4.4.1).

All concomitant medications will be recorded.

The term "study drug" is used throughout this protocol to refer to atezolizumab/placebo. The term "study treatment" refers to all protocol-mandated treatment (atezolizumab/placebo, carboplatin, gemcitabine and capecitabine).

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

Atezolizumab/placebo will be supplied by the Sponsor.

The atezolizumab drug product is provided in a single-use, 20 mL United States Pharmacopeia (USP)/Ph. Eur. Type 1 glass vial as a colourless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab will be administered in 250 mL 0.9% sodium chloride (NaCl) IV infusion bags and infusion lines equipped with 0.2 µm in-line filters. The IV bag may be constructed of polyvinylchloride (PVC) or polyolefin; the IV infusion line may be constructed of PVC or polyethylene; and the 0.2 µm in-line filter may be constructed of polyethersulfone. No incompatibilities have been observed between atezolizumab and these infusion materials (bags and infusion lines).

Atezolizumab vials must be refrigerated at 2°C-8°C (36°F-46°F) upon receipt until use. Vials should not be used beyond the expiration date provided by the manufacturer. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The solution for infusion should be used immediately to limit

microbial growth in case of potential accidental contamination. Any unused portion of drug left in a vial should be discarded. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Further details on the storage and preparation of atezolizumab are provided in the Atezolizumab Investigator's Brochure and the Pharmacy Manual.

4.3.1.2 Placebo

Matching placebo will consist of the vehicle without the antibody. Placebo will be supplied in a single-use, 20 mL USP/Ph. Eur. Type 1 glass vial as a colourless-to-$slightly$-$yellow$, sterile, preservative-free clear liquid solution intended for IV administration. The vial contains ~20 mL of solution. The formulation contains 20 mM histidine acetate, 120 mM sucrose, and 0.04% polysorbate 20, pH 5.8.

Placebo will be stored, handled, and administered as described for atezolizumab. Further details are provided in the Pharmacy Manual.

4.3.1.3 Carboplatin

Carboplatin will be considered an IMP in this study and provided by the Sponsor.

Carboplatin 10 mg/ml Concentrate for Infusion will be supplied in vials containing 150 mg of carboplatin. Carboplatin 10 mg/ml concentrate for solution for infusion is a clear, colourless to faintly yellow solution, free from particles. The vials should not be stored above 25°C.

The product may be diluted with sterile 5% glucose solution for injection or sterile 0.9% NaCl solution for injection up to a final concentration of 0.5 mg/ml (500 micrograms/ml). When diluted as directed, carboplatin solutions should be used within three hours when stored at room temperature (15–25°C) protected from light or within 24 hours when stored at 2–8°C if the ready-to-use solution/dilution has been prepared under validated aseptic conditions. Carboplatin is administered by a short term (15 to 60 minutes) infusion. Needles or intravenous sets containing aluminium parts that may come in contact with carboplatin should not be used for preparation or administration.

For further information on the formulation, packaging, and handling of carboplatin, refer to the current local prescribing information.

4.3.1.4 Gemcitabine

Gemcitabine will be considered an IMP in this study and provided by the Sponsor.

Gemcitabine 38 mg/mL powder for solution for infusion or 38 mg/mL solution will be provided in vials containing 1000 mg gemcitabine. After reconstitution of the powder, one mL contains 38 mg gemcitabine.

The powder-containing vials should not be refrigerated or frozen. The vials with the liquid formulation must be stored refrigerated. After opening, the contents of vials must be reconstituted, and the medicine must be used immediately. Reconstituted gemcitabine solutions should not be kept in a refrigerator, as crystallisation may occur.

The only approved solvent for the reconstitution of the sterile gemcitabine powder and the liquid formulation is sodium chloride 9 mg/mL (0.9%) solution for injection (with no preservatives). For considerations of solubility, the maximum concentration of gemcitabine in

the reconstituted solution is 40 mg/mL. For reconstitution of the powder, the volume of sodium chloride solution to be added to gemcitabine is 25 mL for the 1000 mg dose strength (providing a total volume of 26.3 mL after reconstitution). The reconstituted solution is clear and colourless to slightly yellow.

Further dilution with sodium chloride 9 mg/mL (0.9%) solution for injection without preservatives can be done.

For further information on the formulation, packaging, and handling of gemcitabine, refer to the local prescribing information for gemcitabine.

4.3.1.5 Capecitabine

In this study, the capecitabine dosing regimen (1000 mg/m^2 twice daily on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle) is mandated per protocol. As the recommended starting dose, according to SmPC or prescribing information, is 1250 mg/m^2 twice daily, capecitabine will be considered an IMP in this study, and provided by the Sponsor. For information on the formulation, packaging, and handling of capecitabine, refer to the local prescribing information for capecitabine.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Study treatment will be delivered as follows:

Arm A

Atezolizumab 1200 mg by IV infusion on Day 1 of each 3-week treatment cycle with either:

- gemcitabine 1000 mg/m^2, followed by carboplatin target AUC 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle

or

- capecitabine 1000 mg/m^2 twice daily orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle.

Arm B

Placebo 1200 mg by IV infusion on day 1 of each 3-week treatment cycle with either:

- gemcitabine 1000 mg/m^2, followed by carboplatin target AUC 2 mg/ml/min, both administered by IV infusion on Days 1 and 8 of each 3-week treatment cycle

or

- capecitabine 1000 mg/m^2 twice daily orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle.

Details on treatment administration, including any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.5.

4.3.2.1 Atezolizumab/Placebo

Patients will receive atezolizumab 1200 mg (corresponding to 20 mL from drug product, in 250 mL 0.9% NaCl) or matching placebo by IV infusion administered on Day 1 (± 3 days) of every 21-day cycle.

Administration of atezolizumab or placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For anaphylaxis precautions, see Appendix 6.

Atezolizumab/placebo infusions will be administered per the instructions outlined in **Table 3**. The first dose (Cycle 1, Day 1) will be administered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion of atezolizumab/placebo, no premedication will be administered. However, should the patient experience infusion-related reaction(s) during any infusion, premedication with antihistamines will be administered for subsequent infusions at the discretion of the treating physician.

Table 3 Administration of First and Subsequent Infusions of Atezolizumab / Placebo

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse 20 mL atezolizumab (1200 mg) in 250 mL NaCl) over 60 (± 15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated and after the infusion. • Patients will be informed about the possibility of delayed symptoms following infusion and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered at subsequent infusions at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be administered over 30 (±10) minutes. • If no reaction occurs, subsequent infusions may be administered over 30 (± 10) minutes Continue to record vital signs within 60 minutes before starting infusion and during the infusion if clinically indicated and after the infusion. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (±15) minutes. Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated and after the infusion.

Patients randomised to either group must discontinue all study treatment upon determination of disease progression (PD) per RECIST v1.1. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected. In the absence of disease progression or unacceptable toxicity, study treatment will continue until end of study.

No dose modification for atezolizumab/placebo is allowed. Atezolizumab/placebo and chemotherapy (carboplatin/gemcitabine or capecitabine) may be discontinued for toxicity independently of each other in the absence of PD. Guidelines for medical management of specific adverse events and for atezolizumab/placebo dosing interruption or discontinuation are provided in Section 5.1.4 and Section 5.1.5, respectively.

There is currently no information on overdose with atezolizumab. Any overdose or incorrect administration of the study drug (atezolizumab/placebo) should be noted on the Study Drug

Administration eCRF. Adverse events associated with an overdose or incorrect administration of the study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Carboplatin

In this study, carboplatin will be administered after the completion of gemcitabine administration by short-term IV infusion over 15 to 60 minutes, to target AUC 2 mg/ml/min on Days 1 and 8 of each 3-week treatment cycle.

Patients of certain age groups (i.e., between 40-59 years) and body mass index [BMI] (between 20-25) are at particular risk of undertreatment if glomerular filtration rate (GFR) is estimated using the Cockroft-Gault formula. Given the importance of accurate GFR estimation for optimal efficacy, in such patients, an alternative standard GFR measurement method (inulin, ^{51}Cr-EDTA, ^{99m}Tc-DTPA, ^{125}I-iothalamate or iohexol) should be considered if feasible.

For guidance on carboplatin dose modifications and interruptions due to toxicity, refer to Section 5.1.5.3.2.

There is no known antidote for carboplatin overdose. If necessary, the patient may need supportive treatment relating to myelosuppression, renal, hepatic, and auditory function impairment. Doses up to 1600mg/m^2 have been associated with patients feeling extremely ill with diarrhoea and alopecia developing. Use of higher than recommended doses of carboplatin have also been associated with loss of vision.

For further details, refer to the local prescribing information for carboplatin.

4.3.2.3 Gemcitabine

In this study, gemcitabine will be administered as a 30-minute IV infusion at a dose of 1000 mg/m^2 on Days 1 and 8 of each 3-week treatment cycle. Day 8 infusions should not be administered any earlier than Day 7, but can be administered up to Day 11.

Gemcitabine will be administered after atezolizumab/placebo and will be followed by carboplatin. On Day 1 of Cycle 1 it is recommended to wait at least 30 minutes between each infusion.

Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient; refer to Section 5.1.5.3.3 for details.

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m have been administered by IV infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

For further details, refer to the local prescribing information for gemcitabine.

4.3.2.4 Capecitabine

Capecitabine is available in tablets of 500 mg and of 150 mg. Capecitabine tablets should not be crushed or cut. Patients will be instructed to take capecitabine 1000 mg/m^2 twice daily, approximately 12 hours apart (total daily dose of 2000 mg/m^2) orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle; see **Table 4**. In each cycle, the first dose of capecitabine should be taken in the evening of Day 1, and the last dose in the morning of Day 15. Capecitabine tablets should be taken with water, within 30 min after the end of a meal/snack.

In patients with moderate renal impairment (calculated CrCl of 30–50 mL/min) at baseline, a dose reduction to 75% is recommended for capecitabine; refer to **Table 4** for details.

Table 4 Standard and Reduced Dose Calculations According to Body Surface Area for a Capecitabine 1000 mg/m²

	Full Dose 1000 mg/m²	Number of tablets per administration (morning and evening)		Reduced dose (75%) 750 mg/m²	Reduced dose (50%) 500 mg/m²
BSA (m²)	Dose per administration (mg)	150 mg tablets	500 mg tablets	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1150	1	2	800	600
1.27 – 1.38	1300	2	2	1000	600
1.39 – 1.52	1450	3	2	1100	750
1.53 – 1.66	1600	4	2	1200	800
1.67 – 1.78	1750	5	2	1300	800
1.79 – 1.92	1800	2	3	1400	900
1.93 – 2.06	2000	-	4	1500	1000
2.07 – 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

BSA=Body Surface Area

4.3.3 Additional Medication

Non-investigational medicinal products (NIMPs) used in the study include premedication (see Section 4.4.1.1), medications that may be administered to manage adverse events (see Section 5.1.4), and other permitted concomitant medications (see Section 4.4.1).

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study (atezolizumab/placebo and chemotherapy) will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced and must be reported immediately to the study monitor. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

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

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

Refer to the Pharmacy Manual for further information on IMP handling, storage, and accountability.

4.3.5 Continued (Post-Trial) Access to Atezolizumab

The Sponsor will offer continued access to Sponsor study drug (atezolizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive atezolizumab after completing the study if **all** of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will **not** be eligible to receive atezolizumab after completing the study if **any** of the following conditions are met:

- Atezolizumab is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for mTNBC
- The Sponsor has reasonable safety concerns regarding the drug as treatment for mTNBC
- Provision of the drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening to the treatment

discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Between the treatment discontinuation and the end of study visit, only new anti-cancer treatment will be recorded.

4.4.1 Permitted Therapy

The following therapies are permitted on study:

- Oral contraceptives with a failure rate of < 1% per year; refer to Section 4.1.1.

  Patients who use contraceptives should continue their use during the treatment period and for at least 5 months after the last dose of atezolizumab or 6 months after the last dose of capecitabine, whichever is later; refer to Section 4.1.1.

- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin [LMWH])
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma
- Low-dose corticosteroids (≤10 mg prednisone equivalent per day) administered for orthostatic hypotension or adrenocortical insufficiency
- Patients receiving bisphosphonates or denosumab prior to enrolment: treatment should be maintained during screening and while the patient is actively treated with atezolizumab

  Palliative radiotherapy (e.g., treatment of known bone metastases), provided it does not interfere with assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease). Candidate lesions for radiotherapy must be decided prior to study entry.

  Note: It is not required to hold atezolizumab/placebo during palliative radiotherapy; chemotherapy should be interrupted per institutional standard of care.

- Anticonvulsants at a stable dose are allowed, e.g., for patients with CNS metastases
- Narcotic pain medication is permitted as long as the patient is on a stable regimen at study entry.
- Vaccinations (such as influenza, Covid-19)

  Live, attenuated vaccines are not permitted (see Table 5)

4.4.1.1 Premedication

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 4.4.2) as clinically indicated and per local standards. Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

For the first infusion of atezolizumab/placebo, no premedication will be administered. However, should the patient experience infusion-related reaction(s) during any infusion,

premedication with antihistamines may be administered for subsequent infusions at the discretion of the treating physician.

Nausea and vomiting, which are generally delayed until 6 to 12 hours after administration of carboplatin, may be prevented or controlled with antiemetics. No specific premedication is required prior to the administration of gemcitabine or capecitabine.

Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumour immune activity, it is recommended that the dose of dexamethasone (or equivalent) is minimised such that it does not exceed the equivalent of 10 mg/day of oral prednisone, and as deemed clinically appropriate.

4.4.1.2 Blood Transfusions and G-CSF Use

G-CSF may be administered until 2 weeks prior Cycle 1, Day 1 (to stimulate ANC, or for other purposes). A minimum 14-day washout period between the G-CSF administration and the first dose of study treatment is obligatory to ensure that the patient's bone marrow is sufficiently productive to meet the inclusion criteria and to ensure patient safety during treatment. During study treatment, G-SCF may be used to treat neutropenia in accordance with local practices.

Similarly, a minimum 14-day wash-out period prior Cycle 1, Day 1 should be observed in case a blood transfusion is performed to increase haemoglobin levels before the first dose of study treatment. During study treatment, blood transfusions may be carried out to treat anaemia in accordance with local practices.

4.4.2 Prohibited and Cautionary Therapy

Excessive activation of the immune system is a potential risk associated with atezolizumab and has been observed when atezolizumab is used in combination with other immunomodulating agents. Therefore, the use of these agents is prohibited (i.e., immune checkpoint modulators) or limited (e.g., interferons or IL-2; prohibited within 28 days or 5 half-lives of the drug prior to randomisation, whichever is longer) prior to randomisation, during study treatment, and for 10 weeks after atezolizumab discontinuation.

Medications that are prohibited while the patient is receiving study treatment, and their respective washout periods prior to randomisation are listed in **Table 5**.

Table 5 Prohibited Medications and Treatments

Prohibited Medication/Class	Minimum Washout Period Prior to Randomisation
Any other systemic anti-cancer therapy (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, systemic radiation therapy, and herbal therapy)	28 days or five drug-elimination half-lives of the drug (whichever is longer)
Any investigational therapy	30 days
Immunomodulatory agents, e.g., interferons or IL 2 [a]	28 days or five drug-elimination half-lives of the drug (whichever is longer)
Any live, attenuated vaccine (e.g., FluMist®) [b]	28 days[b]
Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2)	28 days or five drug-elimination half-lives of the drug (whichever is longer)
China population: Chinese traditional medicines with an approved indication for cancer treatment	14 days

a. These agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.

b. Any live, attenuated vaccine is prohibited within 28 days prior to randomisation, during treatment, and within 5 months following the last dose of atezolizumab/placebo.

The above list of medications is not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication and/or contact the Medical Monitor if questions arise regarding medications not listed above.

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy. Guidelines for the management of immune-mediated adverse events are described in Section 5.1.4 and in Appendix 10.

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of atezolizumab. No drug interaction studies have been conducted for atezolizumab, and there are no known PK interactions with other medicinal products.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal

therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.3 Additional Restrictions Related to Chemotherapy

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

- Patients receiving carboplatin/gemcitabine treatment:
  - Concomitant use of yellow fever vaccine is prohibited, and vaccination with other live attenuated vaccine should be avoided;
  - Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished;
  - Concomitant use of phenytoin or fosphenytoin is not recommended due to the risk of exacerbation of convulsions, risk of toxicity enhancement or loss of efficacy of the cytotoxic drug;
  - The concomitant use of the following agents should be approached with caution: (i) ciclosporin, tacrolimus, and sirolimus (risk of excessive immunosuppression); (ii) nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, including loop diuretics (risk of increased, exacerbated, or cumulative toxicity)
  - Concurrent (given together or ≤7 days apart) radiotherapy should be avoided;
  - Carboplatin receiving patients with severe and persistent myelosuppression are at high risk of infectious complications including fatal outcomes. If any of these events occurs, carboplatin should be discontinued.
- Patients receiving capecitabine treatment:
  - Concomitant treatment with sorivudine or its chemically related analogues, such as brivudine is prohibited (contraindication). A minimum 4-week Washout period is required between the end of treatment with sorivudine (or its chemically related analogues) and start of capecitabine therapy;
  - Concomitant use of allopurinol with capecitabine should be avoided;
  - Care should be exercised when capecitabine is co-administered with substrates of the cytochrome P450 2C9 isoenzyme system, such as phenytoin, and coumarin derivative anticoagulants. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations. Patients receiving concomitant capecitabine and oral coumarin derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly;
  - In addition, the concomitant use of the following treatments with capecitabine may be associated with increased toxicity, and should be approached with caution: (i) folinic acid, including folic acid supplementation; (ii) interferon alpha-2a; (iii) radiotherapy;
  - Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. Capectabine tablets should not be crushed or cut.

4.4.4 Prohibited Food

No foods are prohibited during treatment with the study treatments.

Administration with food decreases the rate of capecitabine absorption; therefore, patients should be instructed to administer capecitabine within 30 minutes after a meal.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening test or procedure. Signing of the Informed Consent Form (ICF) can occur more than 28 days before initiation of study treatment. Signed ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomisation (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history, reproductive status, smoking history, and use of alcohol, will be recorded at baseline. TNBC history will include prior cancer therapies, procedures, and an assessment of tumour mutational status (breast cancer susceptibility gene [BRCA] mutational status, where available). In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study drug (Cycle 1, Day 1) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by local law).

4.5.3 Physical Examinations

A complete physical examination must be conducted at screening and the treatment discontinuation visit. Limited, symptom-directed physical examinations should be performed at subsequent postbaseline visits (may be completed ≤ 96 hours of Day 1 treatment; see Appendix 1) and as clinically indicated. Physical examinations will include a review of the main body organs and systems, with special attention to cardiovascular (e.g. abnormally low or irregular pulse, chest pain, tachycardia, swollen legs), respiratory (e.g. shortness of breath,

crackling), gastrointestinal (e.g. abdominal pain, digestive disorders) systems, and a neurological exam focusing on signs and symptoms potentially indicative of disorders such as myasthenia gravis, motor and sensory neuropathy, meningitis, and encephalitis.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

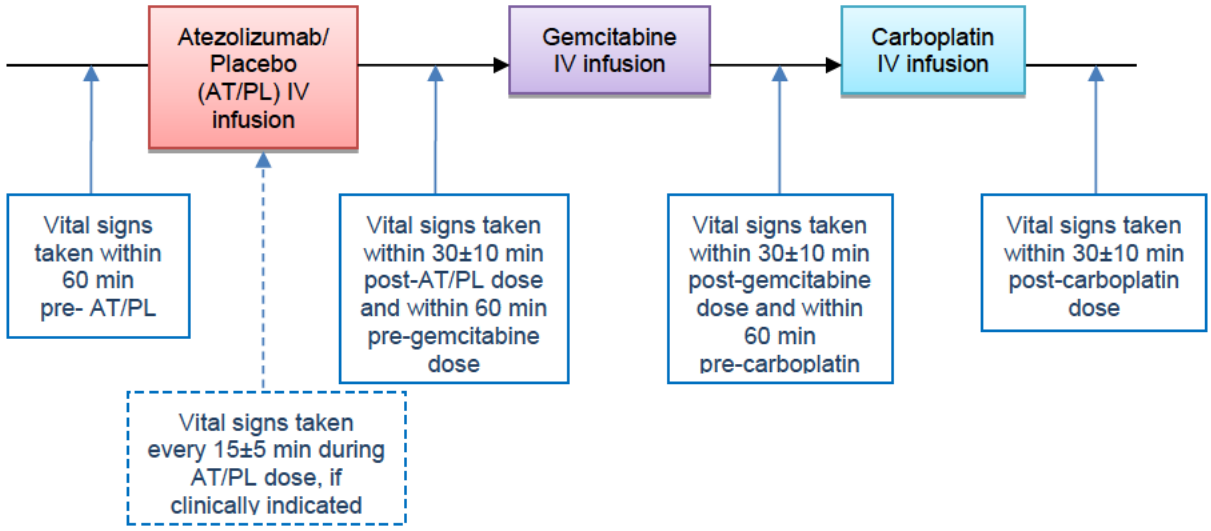
4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

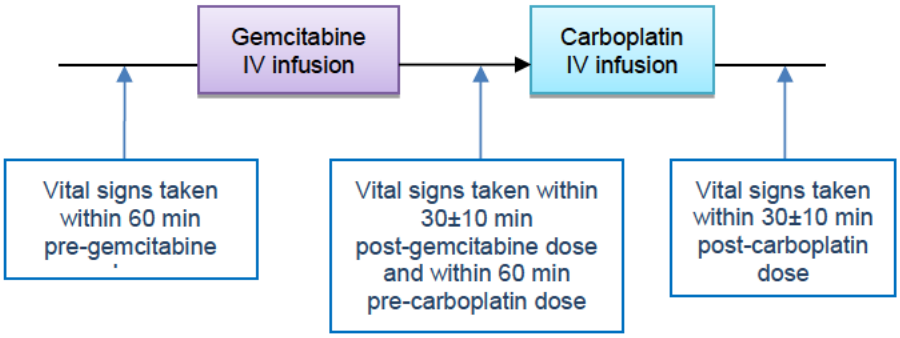
At all clinic visits where study treatment is administered, vital signs should be measured within 60 minutes before and 30 (±10) minutes after each infusion. Vital signs will also be determined every 15 (±5) minutes during the atezolizumab/placebo infusions if clinically indicated (see **Figure 2** and **Table 3**).

Figure 2 Schedule of Vital Sign Assessments Pre- and Post-Infusions

Day 1 of each Cycle:



Day 8 of each Cycle:



4.5.5 Tumour and Response Evaluations

Tumour assessments will be performed at screening (baseline), approximately every 8 weeks (±1 week) for the first 12 months after randomisation, and every 12 weeks thereafter (see Appendix 1) until PD, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. All known sites of disease (measurable and non-measurable) must be documented at screening (baseline) and re-assessed at each subsequent tumour evaluation.

4.5.5.1 Screening (Baseline) Tumour Evaluations

Tumour assessments performed as part of standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used as baseline assessments rather than repeating the tests.

Radiologic imaging performed during the screening period should consist of the following:

1. Initial screening assessments must include CT scans (with oral/IV contrast unless contraindicated) and/or MRI of the chest/abdomen/pelvis. A spiral CT scan of the chest

may be obtained but is not a requirement. MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). If a CT scan for tumour assessment is performed using a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan.

2. Bone scan or PET scan must be performed to evaluate for bone metastases;
3. A CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute a diagnosis of CNS metastasis at screening in the event of an equivocal scan. Patients with active or untreated CNS metastasis are not eligible for this study (see Section 4.1.2 for CNS-related exclusion criteria);
4. CT scans of the neck should also be performed if clinically indicated during the screening period;
5. At the investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used.

4.5.5.2 On-treatment Tumour and Response Evaluations

After randomisation, tumour assessments and evaluation of tumour response per RECIST v1.1 (see Appendix 3) will be performed every 8 weeks (± 1 week) for the first 12 months after treatment initiation and every 12 weeks (± 1 week) thereafter (see Appendix 1) until disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Tumour assessments will be performed according to the specified schedule regardless of dose delays, interruptions or discontinuations. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumour assessments according to the protocol-specified schedule until they experience disease progression, withdraw consent, or die, or until the study closes, whichever occurs first, even if they started another anti-cancer therapy after study treatment discontinuation.

For each patient, the same radiographic procedures and technique used to assess disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans and/or MRI), and results must be reviewed by the investigator before dosing at the next cycle. All known sites of disease documented at screening (baseline) should be re-assessed at each subsequent tumour evaluation. To the extent feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if progressive disease is suspected. If the initial screening bone scan or PET scan does not show evidence of bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion.

Evaluation of tumour response will be completed by the investigator based on physical examinations, CT scans, and other modalities, per RECIST v1.1 (see Appendix 3). An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation.

If treatment is discontinued prior to disease progression per RECIST v1.1 (e.g., due to study treatment-related toxicity), tumour response assessment should continue to be performed per the schedule specified in Appendix 1. During the post-treatment follow-up period, only patients with no documented progressive disease will undergo tumour assessments.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

An overview of the standard safety laboratory, biomarker, and other sampling requirements is provided below. For additional details on laboratory assessments and sample handling, refer to the laboratory manual.

4.5.6.1 Local Laboratory Assessments

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

- Haematology: red blood cell (RBC) count, haemoglobin, haematocrit, white blood cell (WBC) count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), if clinically indicated, and platelet count.
- Serum chemistry: BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate (if part of standard analysis), calcium, phosphorus, glucose, total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), total protein, and albumin. *Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms suggestive of pancreatitis.*

  The Cockcroft-Gault formula (see Appendix 8) will be used to calculate CrCl. Patients must have a CrCl ≥ 30 mL/min to be eligible for enrolment. For patients of certain age groups (i.e., between 40–59 years) and body mass index [BMI] (between 20-25) who are receiving carboplatin, an alternative standard GFR measurement method (inulin, 51Cr-EDTA, 99mTc-DTPA, 125I-iothalamate or iohexol) should be considered if feasible.

  Levels of magnesium and phosphorus must be tested during screening. During treatment, levels of magnesium and phosphorus should be tested as clinically indicated. Glucose levels in diabetic patients receiving capecitabine must be monitored regularly during study treatment in accordance with local standards.
- Coagulation panel: aPTT and INR; performed at screening/baseline, on Day 1 of each cycle (for patients receiving capecitabine), and at treatment discontinuation.
- All women of childbearing potential will have a serum pregnancy test at screening/baseline (within 14 days before Cycle 1, Day 1); after randomisation, urine pregnancy tests will be performed at every cycle and at treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhoea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).
- Thyroid function testing: thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (T4); performed at

screening, on Day 1 of Cycle 1 and every fourth cycle thereafter, and at treatment discontinuation.

In case the results of thyroid function testing are not available by the scheduled study visit, study treatment may be administered as planned, provided that the patient does not exhibit symptoms indicative of thyroid dysfunction. However, the test results should be reviewed by the investigator as soon as they become available, and acted upon, as necessary.

- Urinalysis by dipstick method (pH, specific gravity, glucose, protein, ketones, blood); performed at screening, and during study treatment on Day 1 of Cycle 3 and thereafter as clinically indicated.

Local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

In addition, all patients will undergo the following tests at screening only:

- HIV serology; HIV-positive patients will be excluded from the clinical trial.
- HBV serology: HBsAg, HBsAb, and total HBcAb for all patients; HBV DNA for patients with negative HBsAg and HBsAb tests and a positive total HBcAb test.
- HCV serology: hepatitis C virus antibody (HCVAb) and (if HCV antibody test is positive) HCV RNA. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- Initial confirmation of TNBC (HER2, ER, PR) status (prior to randomisation) may also occur locally. *If local testing is chosen for determination of eligibility, prospective central testing for eligibility purposes should not be requested (retrospective testing for central confirmation of TNBC will be performed but will have no impact on eligibility).*

4.5.6.2 Central Laboratory Assessments

The assessments listed below will be performed at a central laboratory or by the Sponsor. Any residual material from samples collected to enable these central assessments may be used for additional atezolizumab-related safety assessments (e.g., ATA assay), exploratory biomarker profiling, identification, and PD assay development purposes and development and/or improvement of diagnostic tests. Instruction manuals and supply kits will be provided by Covance Inc. for all central laboratory assessments.

4.5.6.2.1 Anti-Drug Antibody Testing

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Serum samples will be assayed for the presence of ADAs to atezolizumab using validated immunoassays at multiple timepoints before, during, and after study treatment (see Appendix 2 for the sampling schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ADA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints, as described in Section 6.8. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

4.5.6.2.2 Pharmacokinetic Testing

Serum samples will be assayed for atezolizumab concentrations (C_{min}, C_{max}) using a validated immunoassay (see Appendix 2 for the sampling schedule).

4.5.6.2.3 Biomarker Assays

Tissue and blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to TNBC or tumour immune biology) from all eligible patients according to the schedule in Appendix 2. Serially collected blood samples will be processed to obtain plasma for the determination of changes in blood-based biomarkers. Whole blood samples may be used to assess germline DNA as a reference for analysis of somatic gene alterations.

Analysis of PD-L1 expression will be performed using the investigational VENTANA PD-L1 (SP142) CDx Assay.

Table 6 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarkers
Plasma (mandatory) [1]	Pre-dose at day 1 of cycles 1, 2 and 3, thereafter every 3 months during treatment and at disease progression	• Immune- or tumour-related proteins
Whole blood sample for germline DNA analysis (DNA extracted from blood), (mandatory) [1]	Baseline	• Germline DNA, e.g. as a reference for analysis of somatic gene alterations • Germline DNA may also be used for clinical genotyping, e.g. analyses of SNPs of interest
ctDNA isolated from plasma [1]	Pre-dose at day 1 of cycles 1, 2 and 3, thereafter every 3 months during treatment and at disease progression	• ctDNA
FFPE Tumour tissue (mandatory)	FFPE tumor specimen (either an archival specimen or freshly collected pre-treatment tissue from relapsed disease) in paraffin block (preferred) or at least 17 unstained slides	• PD-L1 (confirmation of eligibility and stratification factor) prospective assessment by *VENTANA PD-L1 (SP142) Assay* • HER2, ER, PR (prospective or retrospective central confirmation of TNBC for confirmation of target population) • Exploratory assessment of TILs • Exploratory assessment of PD-L1 by *VENTANA PD-L1 (*SP263*)* Assay

Sample Type	Timing	Proposed Biomarkers
		• Exploratory assessment of immune-related proteins such as CD8, CD3, FoxP3, CD68 and others
FFPE Tumour tissue (optional) [1]	On-treatment biopsy within 14 days prior to any treatment (incl. steroid medication) on Day 1 of Cycle 2, and at time of progression (+/- 7days) (optional; preferably from a new or progressing lesion)	• Exploratory assessment of TILs • Exploratory assessment of immune-related proteins, such as CD8, CD3, FoxP3, CD68 and PD-L1 and others • Other markers as applicable
DNA extracted from tumour tissue	See timepoints for tumour tissue collection above	• Somatic gene alterations
RNA extracted from tumour tissue	See timepoints for tumour tissue collection above	• Gene expression signatures

CD: cluster of differentiation; ctDNA: circulating tumour deoxyribonucleic acid; DNA: deoxyribonucleic acid; ER: oestrogen receptor; FFPE: formalin-fixed, paraffin-embedded; FoxP3: Forkhead Box P3 protein (scurfin); HER2: human epidermal growth factor; PR: progesterone receptor; PD-L1: programmed death ligand 1; RNA: ribonucleic acid; SNP: Single Nucleotide Polymorphisms; TILs: tumour-infiltrating-lymphocytes; TNBC: triple-negative breast cancer.

[1] Patients enrolled in mainland China will not undergo the following sample collections:

- Optional FFPE tumour tissue collections on Day 1 of Cycle 2 and at disease progression.
- Collection of whole blood sample for germline DNA analysis on Day 1 of Cycle 1
- Collection of plasma samples for biomarker analysis on Day 1 of Cycles 1, 2, 3, and every 3 months thereafter.

Patients enrolled in mainland China will only contribute to exploratory biomarker analyses that are based on mandatory tumour tissue samples collected at screening. The number of required slides for exploratory analyses using tumor tissue samples are contingent upon the review and approval of the exploratory research by each site's IRB/EC, and upon the review and approval by the Human Genetics Resources Administration of China (HGRAC) exploratory application.

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

4.5.6.2.4 Collection of Tumour Tissue Samples

Serial tumour tissue biopsies will be collected at the following time points to assess changes in the immune tumour-microenvironment by exploratory immune-related biomarker analysis:

- A tumor specimen obtained from relapsed metastatic or locally advanced disease may be submitted, if clinically feasible. If a fresh tumour sample is not clinically feasible, the primary surgical resection sample or the most recent formalin-fixed, paraffin-embedded (FFPE) tumour biopsy sample should be used.
- On-treatment (optional sample; collected within 14 days prior to any treatment [including steroid medication] on Day 1 of Cycle 2)*; and
- At tumour progression (±7 days; optional sample)*.

*Patients enrolled in mainland China will not undergo optional FFPE tumour tissue collections on Day 1 of Cycle 2 and at disease progression.

Collection of Mandatory Tumour Tissue Samples

A representative FFPE tumour specimen block (preferred) or at least 17 unstained slides, with an associated pathology report (if available), must be submitted for centralised determination of PD-L1 status prior to study enrolment. These tumour specimens will also be used for retrospective confirmation of HER2, ER, PR expression by the designated central testing laboratory in cases where initial prospective confirmation of triple-negative tumour status occurred locally. *If local TNBC testing is chosen for determination of eligibility, prospective central testing for eligibility purposes should not be requested (retrospective testing for central confirmation of TNBC will be performed but will have no impact on eligibility).* Acceptable tumour sample collection methods include core needle biopsies for deep tumour tissue (minimum three cores), or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. Tumour tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable. The tumour tissue should be of good quality based on total and viable tumour content. Samples must contain a minimum of 50 viable tumour cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method.

A diagnostic antihuman PD-L1 monoclonal antibody (VENTANA SP142) will be used to stain prospectively for PD-L1 expression on FFPE tumour tissue by IHC, as described in published literature (Herbst et al. 2014; Powles et al. 2014; Schmid et al. 2018). PD-L1 expression on tumour-infiltrating immune cells (IC) will be scored as IC0, 1, 2, or 3 if less than 1%, 1% to less than 5%, 5% to less than 10%, or 10% or greater, respectively IC tumour area stain positive for PD-L1. All types of ICs, including macrophages, dendritic cells, and lymphocytes, will be counted together. Patients will be stratified according to PD-L1 status (PD-L1 IC0 versus PD-L1 IC1/2/3). Patients enrolled as of protocol version 4.0 must have PD-L1-positive tumour status confirmed centrally using the *investigational VENTANA PD-L1 (SP142) Assay* prior to randomisation.

Patients whose tumour tissue is not evaluable for prospective central testing of PD-L1 status are not eligible. Archival or newly collected tumor tissue sample must be submitted. If multiple tumour specimens are submitted, patients may be eligible if at least one specimen is evaluablefor PD-L1 expression (regardless of whether the tissue is from an archival specimen or from relapsed disease). Tissue samples from patients who are not eligible to enrol into the study will be returned no later than 6 weeks after eligibility determination.

Consistent with the exploratory biomarker objectives, the status of immune-related and tumour type-related, and other exploratory biomarkers (including but not limited to immune cell markers, gene alterations and gene expression) in pre-treatment, on-treatment and progressive disease tumour tissue samples of enrolled patients may be evaluated.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analysed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

Collection of Optional Tumour Tissue Samples

For patients who agree to provide optional tumour tissue samples for biopsy by signing the separate Consent for Optional Biopsies form, additional tumour samples may be collected prior to dosing on Cycle 2, Day 1 as per the investigator's discretion. An optional tumour biopsy may also be collected (if clinically feasible and permitted by local guidelines and regulations; preferably from a new or progressing lesion) from consenting patients at first evidence of radiographic disease progression per RECIST v1.1. Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. DNA and RNA sequencing will be performed on these specimens.

Acceptable tumour sample collection methods for optional samples are identical to those for mandatory tumour biopsies at screening.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analysed, unless the patient specifically requests that the samples be destroyed, or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

Patients enrolled in mainland China will not undergo optional FFPE tumour tissue collections.

4.5.6.3 Use and Storage of Remaining Samples from Other Procedures

4.5.6.3.1 Remaining Samples from Study Procedures

Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Unless the patient gives specific consent for his or her unused or leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed 5 years after the final Clinical Study Report has been completed, with the following exceptions:

- For enroled patients, remaining archival/primary resection tissue blocks will be returned to the site upon request or 18 months after clinical closures of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the sites no later than 6 weeks after eligibility determination.

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

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

Samples collected from patients enrolled in mainland China will not be stored for potential future exploratory research.

4.5.7 Electrocardiograms

Single 12-lead ECG recordings will be obtained at screening and may be obtained at unscheduled time-points during study treatment, as clinically indicated; see Appendix 1. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analysed retrospectively at a central laboratory.

Additional cardiovascular monitoring (such as ECG and/or echocardiography) may be considered during the patient's study participation, if clinically indicated by the appearance of symptoms or findings at regular vital sign checks or medical examinations suggestive of cardiovascular disease (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs, shortness of breath, crackling) especially if these cannot be explained by thyroid or electrolyte abnormalities.

4.5.8 Patient-Reported Outcomes

PROs of global health status (GHS)/QoL, function, disease/treatment related symptoms and associated bother, and health utility will be assessed using the EORTC QLQ-C30, QLQ-BR23, FACT-G, and EQ-5D-5L questionnaires, to more fully characterize the clinical profile of atezolizumab plus chemotherapy compared to placebo plus chemotherapy. Sample versions of the PRO instruments are provided in Appendix 4.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff, and completed on paper booklets in their entirety by the patient at the investigational site, both while receiving study treatment and after treatment discontinuation. To ensure instrument validity and that data standards meet health authority requirements, questionnaires must be completed by the patient at the start of the clinic visit before discussion of the patient's health state, laboratory results, or health record; before administration of study treatment; and/or prior to the performance of any other study assessments that could bias the patient's responses. It is common for patients to complete laboratory assessments before a scheduled clinic visit. Completion of PROs after laboratory tests is permitted so long as there is no prior discussion of the patients' laboratory results or health record with clinic staff and that the PROs are completed before drug administration. If the patient is unable to complete the measure on their own, interviewer assessment is allowed but may only be conducted by a member of the clinic staff who reads the questionnaire items to the patient verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the respondent's initials, study patient number and date and time of completion recorded in compliance with good clinical practice. Sites will enter patient responses to the PRO questionnaires into the electronic data capture (EDC) system.

All patients will begin completion of the questionnaires with the EORTC QLQ-C30, followed by the QLQ-BR23, FACT-G single item GP5, and then the EQ-5D-5L at timepoints corresponding with in-clinic visits; both while receiving study treatment and after treatment discontinuation. Refer to Appendix 1 for the frequency and timing of PRO assessments.

4.5.8.1 EORTC QLQ-C30 and QLQ-BR23

The EORTC QLQ-C30 and its breast cancer-specific module, the QLQ-BR23, are validated and reliable self-report measures (Aaronson et al.1993; Sprangers et al. 1996; Osoba et al. 1997; Osoba et al. 1998). The EORTC QLQ-C30 (version 3) consists of thirty questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social); eight symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea; global health status/quality of life (GHS/QoL), and financial difficulties, with a recall period of "the last week". Scale scores are obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the global health status and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The QLQ C30 module takes approximately 10 minutes to complete.

The breast cancer-specific QLQ-BR23 module consists of 23 additional items assessing disease/treatment symptoms (systemic therapy side effects, breast symptoms, arm symptoms, and hair loss) and aspects of patient functioning (body image, sexual functioning, and future perspective). As the QLQ BR23 was not developed or tested and validated with men, male patients in this study will not complete the QLQ-BR23 measure. The QLQ-BR23 takes approximately 5 minutes to complete.

4.5.8.2 FACT-G Single Item GP5

The Functional Assessment of Cancer Therapy – General (FACT-G) is a validated, 27-item, general quality of life instrument comprised of four subscales (physical, social/family, emotional, and functional well-being) (Cella et al. 1993; Cella 1997). In this study, the single item GP5 ("I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G has been selected for individual item analysis to document the level of treatment side-effect bother on patient's lives. Patients will assess how true the statement "I am bothered by side effects of treatment" has been for them in the previous 7 days on a 5-point scale (0, not at all; 1, little bit; 2, somewhat; 3, quite a bit; 4, very much). The single item GP5 from the FACT G takes less than a minute to complete.

4.5.8.3 EQ-5D-5L

The EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), is a validated, generic, preference-based self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group, 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the

EuroQol EQ-5D: a health state profile that contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013), and a visual analogue scale (VAS) that records the respondent's self-rated health on a scale from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction. The EQ-5D-5L takes approximately 3 minutes to complete. It will be utilised in this study to inform pharmacoeconomic evaluations.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualised drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following optional samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab and locally advanced or metastatic TNBC: leftover or unused FFPE tissue and plasma, whole blood samples and derivatives thereof (e.g. RNA, DNA).

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analysed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development. For sampling procedures, storage conditions, and shipment instructions, refer to the Laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

RBR specimens will not be collected from patients enrolled in mainland China.

4.5.9.4 Confidentiality

RBR samples and associated data will be labelled with a unique patient identification number.

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

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

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.9.5 Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The investigator or authorised designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent/Withdawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com A patient's withdrawal from Study MO39193 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MO39193.

4.5.9.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorised use of specimens as specified in this protocol and in the ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.5.9.8 Long-Term Storage

All blood and tissue samples collected in this study and derivatives thereof will be destroyed no later than 5 years after the date of final closure of the clinical study database. However, patients who enrol in this study will have the option, at the time of enrolment, to consent to RBR sampling to allow the remainder of these samples and derivatives thereof to be stored and used for exploratory research. If the patient provides consent for this optional exploratory research, these samples will be sent to and stored in the RBR and will be destroyed no later than 15 years after the date of final closure of the clinical study database.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to the study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontination is in the best interest of the patient
- Use of another systemic anti-cancer therapy not allowed by the protocol
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per investigator assessment according to RECIST v1.1.

Guidelines for discontinuing study drug for patients who experience specific adverse events are provided in Section 5.1.

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

Patients will return to the clinic for a treatment discontinuation visit 30 (± 5) days after the last dose of study treatment (see Appendix 1 for additional details). After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 21 days) until death (unless the patient withdraws consent, or the Sponsor terminates the study).

Refer to the schedule of activities (see Appendix 1) for details on follow-up assessments to be performed for patients who permanently discontinue study treatment.

4.6.2 Patient Discontinuation from the Study

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance
- Study termination or site closure

Every effort should be made to obtain a reason for patient discontinuation from the study. Patients will return to the clinic for a treatment discontinuation visit at 30 ± 5 days after the last dose of study drug. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status. However, patients will not be followed for any reason after consent has been withdrawn.

Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled).

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 General Plan to Manage Safety Concerns

Atezolizumab (Tecentriq) is approved in several countries around the world for the treatment of urothelial carcinoma, NSCLC, SCLC, TNBC, hepatocellular carcinoma, and melanoma.

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks for atezolizumab are outlined in Section 5.1.2 below. Please refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. These include stringent eligibility criteria (see Section 4.1.1 and Section 4.1.2), designed to exclude patients at higher risk for toxicities, administration of the study drug in a controlled setting, and close safety monitoring of patients during the study (see Section 4.5), including assessment of the nature, frequency, and severity of adverse events (see Section 5.3.3). Administration of study treatment will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

General safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol specified physical examinations, ECGs and safety laboratory assessments (including serum chemistries and blood counts), measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study; see

Appendix 1 for the list and timing of study assessments. Laboratory values must be reviewed prior to each infusion. During physical examinations, special attention will be paid to cardiovascular (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs), respiratory (e.g., shortness of breath, crackling), gastrointestinal (e.g., abdominal pain, digestive disorders) systems, and a neurological exam focusing on signs and symptoms potentially indicative of disorders such as myasthenia gravis, motor and sensory neuropathy, meningitis, and encephalitis. Throughout the study, patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection.

After initiation of study drug, all adverse events (regardless of relationship to study drug) will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab/placebo or until initiation of new systemic anti-cancer therapy, whichever occurs first; refer to Section 5.3.1. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug; refer to Section 5.3.1 for further details. Adverse events will be defined and graded according to NCI CTCAE v4.0. All serious adverse events and protocol defined events of special interest will be reported in an expedited fashion (see Section 5.2.2 and Section 5.2.3, respectively).

Guidelines for management of specific adverse events are provided in Section 5.1.4 and Appendix 10. Guidelines for study treatment dosage modifications, interruptions, or discontinuations due to toxicity are provided in Section 5.1.5. In addition, an iDMC has also been incorporated into the study design to periodically review aggregate safety data (for further details, refer to Section 3.1.2 and the iDMC Charter).

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

This is a double-blind study. Emergency unblinding by the investigator should be performed only in cases when knowledge of treatment assignment will affect the management of a patient who experiences a treatment emergent adverse event; refer to Section 4.2.3 for details.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.2 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. To date, immune mediated adverse events associated with atezolizumab include IRRs, hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions; refer to Section 5.2.3. *In addition,* immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Additional details regarding the anticipated safety risks for atezolizumab clinical safety are provided in Appendix 10 and in the Atezolizumab Investigator's Brochure.

Although most immune mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognised early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup and management of procedures for suspected immune mediated adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure and Appendix 10.

5.1.3 Risks Associated with Chemotherapy

5.1.3.1 Carboplatin

Warnings and precautions related to carboplatin use include:

- Myelosuppression (closely related to the renal clearance of the drug), with median day of nadir reported as Day 21 in patients receiving single agent carboplatin and Day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. Peripheral blood counts, renal and hepatic function tests should be monitored closely during carboplatin treatment.
- Allergic reactions: as with other platinum-based drugs, allergic reactions appearing most often during administration may occur and necessitate discontinuation of infusion. Patients should be observed carefully and an appropriate symptomatic treatment (including antihistamines, adrenaline and/or glucocorticoids) must also be initiated in such cases;
- Renal toxicity (with higher incidence and severity in patients with pre-existing impairment in renal function or previous nephrotoxicity as a result of cisplatin therapy);
- Haemolytic anaemia with the presence of serologic drug-induced antibodies has been reported, and may be fatal;
- Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments;
- Haemolytic-uraemic syndrome (HUS): Carboplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia (rapidly falling haemoglobin with concomitant thrombocytopaenia, elevation of serum bilirubin, serum

creatinine, blood urea nitrogen, or LDH). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required;

- Neurologic toxicity: may manifest as peripheral neurologic toxicity (generally common, but mild), or visual disturbance or loss of vision (generally associated with higher than recommended doses or renal impairment, and appears to resolve within weeks of stopping carboplatin);
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES): a rare, reversible (after treatment discontinuation), rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances;
- Venoocclusive liver disease: Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases;
- Tumour lysis syndrome (TLS): In post-marketing experience TLS has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with high proliferative rate, high tumour burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken;
- Auditory defects/ototoxicity;
- Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents such as carboplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Very common (frequency ≥ 1 per 10 exposed patients) adverse reactions associated with carboplatin include the following (listed by preferred term): thrombocytopaenia, neutropoenia, leucopoenia, anaemia, vomiting, nausea, abdominal pain, creatinine renal clearance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased.

For further details on the risks, including adverse reactions associated with carboplatin treatment, refer to the current local prescribing information for carboplatin.

5.1.3.2 Gemcitabine

Warnings and precautions related to gemcitabine use include:

- Myelosuppression, manifested by leucopoenia, thrombocytopaenia and anaemia (mostly affects the granulocyte count), is usually mild to moderate, short lived and does not result in dose reduction and rarely in discontinuation. However, in some patients, peripheral blood counts may continue to deteriorate after gemcitabine administration;
- Exacerbation of underlying hepatic insufficiency (e.g., in patients with liver metastases);

- Risk of cardiac and/or vascular disorders (such as arrhythmias, heart failure, myocardial infarcts, peripheral vasculitis, gangrene, thrombotic microangiopathy);
- Capillary leak syndrome (CLS), a potentially fatal condition clinically manifested by generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal impairment, and pulmonary oedema, and may lead to adult respiratory distress syndrome (ARDS);
- PRES: most common manifestations include acute hypertension and seizure activity, but other symptoms such as headache, lethargy, confusion, and blindness could also be present. Diagnosis is optimally confirmed by MRI. PRES is typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued, and supportive measures implemented, if PRES develops during therapy;
- Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis, ARDS, pulmonary eosinophilia) have been reported in association with gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition;
- HUS (rare side effect): gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia (see description above). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required;
- Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and nonconcurrent use of gemcitabine;
- Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine.

Additional potentially serious or life-threatening adverse reactions associated with gemcitabine include severe skin reactions, including desquamation and bullous skin eruptions, Stevens-Johnson Syndrome, or TEN, as well as sepsis, and anaphylactoid reactions.

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% patients; dyspnoea reported in 10%–40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients. The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses. Dose-limiting adverse reactions are very common (frequency ≥ 1 per 10 exposed patients), and include reductions in thrombocyte, leucocyte (neutropoenia Grade 3: 19.3%; Grade 4: 6%) and granulocyte counts. Other very common adverse reactions include alopecia, oedema/peripheral oedema, including facial oedema (usually reversible after stopping treatment), and influenza-like symptoms (most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia; cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported).

For further details on the risks, including adverse reactions associated with gemcitabine treatment, refer to the current local prescribing information for gemcitabine.

5.1.3.3 Capecitabine

Warnings and precautions related to capecitabine use include:

- Dose limiting toxicities include diarrhoea (with the risk of dehydration), abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysaesthesia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced;

  Grade 1 hand-foot syndrome is characterised by any of the following: numbness, dysesthesia/paraesthesia, tingling, painless swelling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

- Cardiotoxicity: cardiac arrhythmias (including ventricular fibrillation, torsade de pointes, and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving capecitabine;
- Hepatic impairment: treatment-related elevations in bilirubin or in hepatic aminotransferases (ALT, AST);
- Increased risk of adverse reactions in patients with moderate renal impairment (CrCl of 30–50 ml/min);
- Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhoea, mucosal inflammation, neutropoenia and neurotoxicity) associated with 5-fluorouracil (5-FU) has been attributed to a deficiency of DPD activity. Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil;
- Ophthalmological complications (e.g., keratitis and corneal disorders);
- Severe skin reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN);
- Interactions with sorivudine and analogues, coumarin-derivative anticoagulants, phenytoin, allopurinol, and other agents (see Section 4.4.3);
- In addition, caution must be exercised in patients with central or peripheral nervous system disease (e.g., brain metastasis or neuropathy), pre-existing hypo- or hypercalcaemia, diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment.
- Lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption

Patients should not become pregnant during or within 6 months after the last dose of capecitabine, and should not breastfeed during or within 2 weeks after the last dose of capecitabine.

The most commonly reported and/or clinically relevant treatment-related adverse drug reactions were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysaesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

In case of exposure to crushed or cut capecitabine tablets, the following adverse drug reactions have been reported: eye irritation, eye swelling, skin rash, headache, paraesthesia, diarrhoea, nausea, gastric irritation, and vomiting.

For further details on the risks, including adverse reactions associated with capecitabine treatment, refer to the current local prescribing information for capecitabine.

Patients will be monitored for chemotherapy-related adverse events throughout the study.

5.1.4 Management Guidelines for Specific Adverse Events

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 recognised 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.

For details on the management of infusion-related reactions and all other immune related adverse events, including but not limited to, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic, or eye toxicity, refer to Appendix 10 and the current Atezolizumab Investigator's Brochure.

5.1.4.1 Pulmonary events

5.1.4.1.1 Atezolizumab

Management guidelines for pulmonary events are provided in Appendix 10 and the current Atezolizumab Investigator's Brochure.

5.1.4.1.2 Chemotherapy

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or ARDS) have been reported in association with gemcitabine therapy. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition. Refer to the local gemcitabine prescribing information for further details.

5.1.4.2 Infusion-Related Reactions

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with

supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 6).

5.1.4.2.1 Atezolizumab

No premedication is indicated for the administration of atezolizumab in Cycle 1. However, patients who experience an IRR or CRS with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs or CRS are provided in Appendix 10 and the Atezolizumab Investigator's Brochure.

5.1.4.2.2 Chemotherapy

Carboplatin/gemcitabine should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications.

As with other platinum-based drugs, allergic (hypersensitivity) reactions associated with carboplatin occur most often during administration and necessitate discontinuation of infusion. Anaphylactic-type reactions, sometimes fatal, may occur in the minutes following injection of the product. Patients should be observed carefully and an appropriate symptomatic treatment (including antihistamines, adrenaline and/or glucocorticoids) must be initiated in such cases, as per the local prescribing information for carboplatin.

Allergic skin rashes occur in approximately 25% of patients receiving gemcitabine, and are associated with itching in 10% of patients. However, anaphylactoid reactions associated with gemcitabine infusions are very rare (occurring in <1 per 10,000 exposed patients).

5.1.4.3 Other Adverse Reactions

5.1.4.3.1 Atezolizumab

Refer to Appendix 10 and the Atezolizumab Investigator's Brochure for guidance.

5.1.4.3.2 Chemotherapy

Refer to the respective local prescribing information for guidance.

5.1.5 Dose Modifications and Interruptions due to Adverse Events

5.1.5.1 General Considerations

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

When several toxicities with different grades of severity occur at the same time, the dose interruptions or modifications should be according to the highest grade observed.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab/placebo or chemotherapy) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

Dose reduction of atezolizumab/placebo is not permitted. When treatment is temporarily interrupted because of toxicity caused by atezolizumab/placebo or chemotherapy, the treatment cycles will be restarted such that the atezolizumab/placebo and chemotherapy infusions/administrations remain synchronised.

If it is anticipated that carboplatin/gemcitabine or capecitabine will be delayed by ≥ 2 weeks, then atezolizumab/placebo should be given without the chemotherapy, as long as there is no contraindication. If a delay of more than two consecutive cycles (42 days) is required for recovery for any haematologic or non-haematologic toxicity and/or more than two dose reductions are necessary, gemcitabine and carboplatin should be permanently discontinued. However, if toxicity can be clearly attributable to a single chemotherapy agent (i.e., either carboplatin or gemcitabine), then the investigator can determine whether to stop both agents or continue with one of the two chemotherapy agents (i.e., carboplatin or gemcitabine) alone.

In general, the start of a cycle may be delayed to allow recovery from toxicities, but there should be no delays within cycles. Cycle length is fixed at 21 days, and dosing on Day 8 of a cycle may be skipped but should not be delayed outside of the +3 days window.

The treating physician may use discretion in accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient.

If one component of the study treatment (i.e., atezolizumab/placebo or chemotherapy) is discontinued permanently, treatment with the other drugs may be continued for patients experiencing clinical benefit as determined by the investigator.

For guidelines on the management of patients who experience adverse events, refer to Section 5.1.4 and Appendix 10.

5.1.5.2 Events Requiring Permanent Treatment Discontinuation

5.1.5.2.1 Atezolizumab/Placebo

Atezolizumab/placebo should be discontinued in case of the following events:

- Recurrent pneumonitis (any grade), Grade 2 pulmonary event that has not resolved to Grade ≤1 within 12 weeks, recurrent Grade 2 pulmonary event, or any Grade 3 or 4 pulmonary event;
- Grade 2 hepatic event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 hepatic event;
- Grade 2 or 3 diarrhoea or colitis that has not resolved to Grade ≤1 within 12 weeks, or any Grade 4 diarrhoea or colitis;
- Uncontrolled symptomatic hypothyroidism or hyperthyroidism without thyroid function improvement with treatment;
- Grade 2 to 4 symptomatic adrenal insufficiency that has not resolved to Grade ≤1 or patient is not stable on replacement therapy within 12 weeks;
- Grade 3 or 4 hyperglycemia that has not resolved, or glucose levels are unstable;
- Grade 2 ocular event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 ocular event;

- Grade 2 to 4 immune-mediated myocarditis
- *Grade 2 to 4 immune-mediated pericardial disorders*
- Grade 3 dermatologic event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 4 dermatologic event, or confirmed diagnosis of Stevens Johnson syndrome or toxic epidermal necrolysis (any grade);
- Any Grade 3 or 4 infusion-related reaction;
- Immune mediated meningoencephalitis (any grade);
- Grade 3 or 4 amylase and/or lipase elevation or Grade 2 or 3 immune mediated pancreatitis that has not resolved to Grade ≤1 within 12 weeks; or Grade 4 immune mediated pancreatitis;
- Grade 2 immune-mediated neuropathy that has not resolved to Grade ≤1 within 12 weeks *or Grade 2 facial paresis that has not resolved fully within 12 weeks*; any Grade 3 or 4 immune-mediated neuropathy *(including facial paresis)*; myasthenia gravis or Guillain-Barre syndrome (any grade); *Grade 2 to 4 immune-mediated myelitis*
- Any Grade 2 or 3 hypophysitis that does not resolve to Grade ≤1 within 12 weeks, or Grade 4 hypophysitis;
- Grade 2 renal event that has not resolved to Grade ≤1 within 12 weeks; any Grade 3 or 4 renal event;
- Grade 2 or 3 immune-mediated myositis that has not resolved to Grade ≤1 within 12 weeks; any Grade 4 immune-mediated myositis;
- Suspected HLH or MAS;
- Other events, as detailed in the current Appendix 10 and in the Atezolizumab Investigator's Brochure.

In all the above listed cases, resumption of atezolizumab may be considered for patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed. In case of patients receiving steroids for management of immune-mediated adverse events, atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced/tapered to ≤10 mg/day oral prednisone or equivalent. The acceptable length of interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

For further details, including complete management guidelines for the above listed and additional immune-mediated events, refer to the current Atezolizumab Investigator's Brochure.

5.1.5.2.2 Carboplatin/Gemcitabine

Carboplatin and gemcitabine infusions should be discontinued immediately in case of severe hypersensitivity reaction, and at first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH (risk of HUS).

In addition, carboplatin infusions should be permanently discontinued in case of severe and persistent myelosuppression, or severe impairment in renal or hepatic function.

Development of any of the following events require permanent discontinuation of gemcitabine treatment:

- Capillary leak syndrome (CLS)
- Posterior reversible encephalopathy syndrome (PRES)
- Severe pulmonary effects, such as pulmonary oedema, interstitial pneumonitis or ARDS;
- Severe and persistent myelosuppression.

5.1.5.2.3 Capecitabine

Capecitabine should be permanently discontinued in case any of the following events due to capecitabine develop during treatment:

- Any Grade 4 adverse event (first occurrence);
- Third appearance of any Grade 3 adverse event;
- Fourth appearance of any Grade 2 adverse event;
- If the calculated CrCl decreases to a value below 30 mL/min;
- Development of symptoms suggestive of overdose, such as in patients with unrecognised complete DPD deficiency;
- Severe skin reactions, such as Stevens-Johnson syndrome or TEN.

5.1.5.3 Dose Modifications and Interruptions

5.1.5.3.1 Atezolizumab/Placebo

Dose reduction of atezolizumab/placebo is not permitted in this study.

Atezolizumab/placebo treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to the equivalent of $\leq$ 10 mg/day oral prednisone before atezolizumab/placebo can be resumed. If atezolizumab/placebo is withheld >12 weeks after event onset, the patient will be discontinued from atezolizumab/placebo However, atezolizumab/placebo may be withheld for $>$ 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab/placebo can be resumed after being withheld for $>$ 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab/placebo should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab/placebo treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

5.1.5.3.2 Carboplatin Infusions

Reduction of the initial dosage by 20 - 25% is recommended for those patients who present with risk factors such as prior myelosuppressive treatment and low performance status. Patients with CrCl values below 60 ml/min are at increased risk of severe myelosuppression (Carboplatin SmPC).

Leucopoenia, neutropoenia, and thrombocytopaenia are dose-dependent and dose-limiting toxicities of carboplatin. Therapy should not be repeated until the neutrophil count is at least 2,000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3 (Carboplatin SmPC); refer to **Table 7** for details.

If a delay of more than two consecutive cycles (42 days) is required for recovery for any haematologic or non-haematologic toxicity and/or more than two dose reductions are necessary, gemcitabine and carboplatin should be permanently discontinued. However, if toxicity can be clearly attributable to a single chemotherapy agent (i.e., either carboplatin or gemcitabine), then the investigator can determine whether to stop both agents or continue with one of the two chemotherapy agents (i.e., carboplatin or gemcitabine) alone. No dose re-escalation is allowed after a dose reduction.

5.1.5.3.3 Gemcitabine Infusions

Gemcitabine dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld (until toxicity has resolved in the opinion of the physician) or the dosage decreased depending on the judgement of the treating physician.

For haematological toxicity, dose modifications of gemcitabine within a cycle should be performed according to **Table 7**. Patients should have an absolute granulocyte count of at least 1,500 x 10^6/L and platelet account of 100,000 x 10^6/L prior to the initiation of each cycle.

Table 7 Dose Modification for Gemcitabine and Carboplatin Given in Combination

Absolute Granulocyte Count (x 10^6/L)	Platelet Count (x 10^6/L)	Percentage of Standard Dose for Carboplatin and Gemcitabine (%)
≥ 2000 and	≥ 100,000	Carboplatin: 100% Gemcitabine: 100%
> 1500 to < 2000 and	≥ 100,000	Carboplatin: Omit dose [a] [b] Gemcitabine: 100%
1000 to 1500 or	75,000 to 100,000	Carboplatin: Omit dose [a] Gemcitabine: 50%
< 1000 or	< 75,000	Carboplatin: Omit dose [a] Gemcitabine: Omit dose [c]

a. Carboplatin treatment omitted will not be reinstated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 2,000 x 10^6/L and the platelet count reaches 100,000 x 10^6/L.

b. There may be exceptional cases where a patient with ANC >1500 x 10^6/L and platelet count ≥100,000 x 10^6/L is considered eligible, by the treating physician, to receive carboplatin. In these cases, if there is no evidence of fever or infection, and after careful consideration of the benefit-risk ratio, the investigator may decide to administer the carboplatin dose. The patient should be carefully monitored.

c. Gemcitabine treatment omitted will not be reinstated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 x 10^6/L and the platelet count reaches 100,000 x 10^6/L.

For subsequent cycles, the gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

- Absolute granulocyte count < 500 x 106/L for more than 5 days
- Absolute granulocyte count < 100 x 106/L for more than 3 days
- Febrile neutropoenia
- Platelets < 25,000 x 106/L
- Cycle delay of more than 1 week due to toxicity.

5.1.5.3.4 Capecitabine

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, such as alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption.

Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs.

Doses of capecitabine omitted for toxicity are not replaced. Once the dose has been reduced, it should not be increased at a later time.

General recommendations for capecitabine dose modifications for toxicity are detailed in **Table 8**.

Table 8 Capecitabine Dose reduction Schedule

Toxicity Grades [a]	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 1	Maintain dose level	None (100%)
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	None (100%)
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75%
2nd appearance		50%
3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4		
1st appearance	Discontinue treatment permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

Toxicity Grades [a]	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
2nd appearance	Discontinue treatment permanently	Not applicable

a. According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, Version 4.0.

If Grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased.

Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of > 3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur. Treatment with capecitabine monotherapy may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Patients should also be instructed to stop taking capecitabine and call their physician immediately if they develop any, but not limited to of the following events:

- Grade ≥ 2 hand-foot syndrome (painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patients' activities of daily living;
- Grade ≥ 2 diarrhoea (an increase of 4 to 6 stools/day or nocturnal stools) or severe bloody diarrhoea with severe abdominal pain and fever;
- Grade ≥ 2 dehydration (treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled);
- Grade ≥ 2 nausea (food intake significantly decreased but able to eat intermittently) and/or grade ≥2 vomiting (2 to 5 episodes in a 24-hour period);
- Grade ≥ 2 stomatitis (painful erythema, oedema or ulcers of the mouth or tongue, but able to eat);
- Grade ≥ 2 chest pain (pain localised to the centre of the chest, especially if it occurs during exercise)
- Steven-Johnson syndrome (painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever)
- Angioedema (swelling mainly of the face, lips, tongue or throat which makes it difficult to swallow or breathe, itching and rashes)

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patientadministered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.8 and Section 5.3.5.9 for more information);
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline;
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug;
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death);
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death);

  Note: This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10);
- 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 congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug;
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

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 NCI CTCAE; see Section 5.3.3); 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 eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.5.1)
- Suspected transmission of an infectious agent by the study drug, 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 the study drug is suspected.

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune haemolytic anaemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Myositis
- Myopathies, including rhabdomyolysis
- *Myelitis*
- *Facial paresis*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 (immediate reporting), Section 5.5 (follow-up), and Section 5.6 (events occurring after the reporting period).

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events (regardless of relationship to study drug) will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab/placebo or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting (defined as 90 days after the last dose of atezolizumab/placebo) period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. **Table 9** will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

d. Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2. Deaths that are attributed by the investigator solely to progression of mBC should be recorded only on the Study Discontinuation eCRF (see Section 5.3.5.7).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" to the question: “Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?”

A guide to the interpretation of this causality question is found in Appendix 9.

Causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed

hypersensitivity reactions, sepsis, or infections, HLH, tumour lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study drug infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome"). Ambiguous terms such as "systemic reaction" should be avoided. Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF.

If a patient experienced both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 10.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal 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 neutropoenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for 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 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be 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 Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5.1 Abnormal Liver Function Tests

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. All deaths that are attributed by the investigator solely to progression of mTNBC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept

on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Reporting of deaths that occur after the adverse event reporting period is described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.9 Lack of Efficacy or Worsening of Breast Cancer

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.

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for outpatient care outside of normal outpatient clinic operating hours that is required per protocol or per local standard of care.

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

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

1. Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
2. Medication error: accidental deviation in the administration of a drug

   In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events.

No safety data related to overdosing of atezolizumab are available.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF and reported as a protocol deviation.

Each adverse event associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. **Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.**

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

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

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

address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events and adverse events of special interest that occur after the adverse event reporting period (defined as 90 days after the last dose of atezolizumab/placebo) are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study (with any study treatment) or within **5 months** after the last dose of atezolizumab or within **6 months** after the last dose of capecitabine, whichever is later. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancies should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the foetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will update the Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within **3 months** after the last dose of capecitabine or **6 months** after the last dose of carboplatin/gemcitabine, whichever is later. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information pregnant partner and the on the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofoetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofoetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome, by following the reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

As described in Section 5.3.1, after initiation of study drug, all adverse events (regardless of relationship to study drug) will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab/placebo or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug.

After the end of the adverse event reporting period (defined as 90 days after the last dose of the study drug), during survival follow-up, all deaths, regardless of cause, should be reported through use of the Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

- Atezolizumab Investigator's Brochure
- Local prescribing information/Summary of Product Characteristics (SmPC) for each chemotherapy agent:
  - Carboplatin SmPC
  - Gemcitabine SmPC
  - Capecitabine SmPC

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

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favour the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a phase III, global, double-blind, placebo-controlled, randomised study to evaluate the efficacy and safety of atezolizumab with chemotherapy compared with placebo with chemotherapy in patients with *locally advanced or metastatic* TNBC. Eligible patients will have a local or metastatic recurrence not amenable to treatment with curative intent and must not have received prior chemotherapy for this condition. In addition, patients must have progressed within 12 months from the last treatment with curative intent for their eBC.

Protocol version 4.0 introduced continuation of enrolment of approximately 190 additional (PD-L1-positive only) patients, after the initially planned approximately 350 all-comers (PD-L1-positive and PD-L1-negative) have been randomised. Recruitment of all-comers was closed after 382 all-comers were randomised in the Global study; of these, 140 (36.6%) had PD-L1-positive tumour status.

The analysis populations are defined as follows:

- Modified ITT (mITT) population: all patients randomised in the study before protocol version 4.0 (referred to as all-comers, i.e., PD-L1-positive and PD-L1-negative patients), grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- Full Analysis Set (FAS) population: all patients randomised in the study, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- PD-L1-positive population: all patients randomised in the study whose PD-L1 status was IC1/2/3 at the time of randomisation, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- PD-L1-negative population: all patients randomised in the study whose PD-L1 status was IC0 at the time of randomisation, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- Response-evaluable population: patients randomised in the study with measurable disease at baseline.
- DoR-evaluable population: patients randomised in the study with measurable disease at baseline and an objective response.
- Safety population: patients who received any amount of any study drug.

For all efficacy analyses, patients will be grouped according to the treatment assigned at randomisation. For all safety analyses, patients will be grouped according to the treatment actually received, including cases in which atezolizumab was received in error.

Hypothesis tests will be two-sided unless otherwise indicated. The type I error (α) for this study is 0.05 (two-sided).

Further details of the analyses will be provided in the SAP.

A separate analysis will be performed for the China population (i.e., patients enrolled from China in the Global study and additional China enrolment phase).

Details for the analyses based on the China population will be included in the SAP for the Global study.

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to evaluate the efficacy of atezolizumab plus chemotherapy versus placebo plus chemotherapy in patients with early-relapsing (<12 months) inoperable *locally advanced or metastatic* TNBC as measured by OS.

Patients with TNBC whose disease has progressed within 12 months from their early breast cancer (eBC) treatment are typically excluded from treatment trials. However, retrospective analyses of OS in patients with triple-negative disease have found medians of 8 months (interquartile range: 3, 18) and approximately 11 months (interquartile range: 5, 20) in the relapsed vs de novo cohorts, respectively (den Brok et al. 2017). Notably, the TNBC populations in these studies included patients whose disease had progressed >12 months after (neo)adjuvant treatment. Based on these data in TNBC populations unselected for time to first relapse and the advice of clinical experts with active treatment practices that include patients with TNBC, an estimated median OS of 9.0 months was selected for the control arm of this study.

In order to control for the overall type I error at two-sided 5%, the primary OS endpoint will be evaluated hierarchically in the following fixed order: (1) OS in the PD-L1-positive population, followed by (2) OS in the mITT population.

Based on the estimated median OS of 9 months in the control arm (assuming a similar median OS in the PD-L1-positive and mITT populations based on available data), and a 1:1 randomisation ratio, 247 OS events are required to detect a target HR of 0.70 (3.8-month improvement in median OS) with the addition of atezolizumab to chemotherapy, with 80% power by two-sided log-rank test at an alpha level of 0.05. The expected study recruitment rate is approximately 20 all-comer patients per month. Of the 382 'all-comers' enrolled in the Global study, approximately 37% (N=140) were found to have PD-L1-positive tumour status. Subsequent recruitment will continue only in patients with PD-L1-positive tumour status, for approximately 190 additional patients randomised, in order to achieve the target sample size of 330 patients and the required 247 events for the primary OS analyses in PD-L1 positive population.

The overall study population is estimated at approximately 572 patients (382 all-comers plus approximately 190 additional patients with PD-L1-positive tumour status).

Refer to **Table 10** for further details.

Table 10 Operating Characteristics

Sample Size Calculation Parameters	Values	
	PD-L1-positive Population [1]	mITT Population [2]
Randomisation ratio (*atezolizumab + chemotherapy vs. placebo + chemotherapy*)	1:1	
Expected median OS, Control arm	9 months	
Target HR (hazard ratio), of Atezolizumab vs. Control	0.7	
Type 1 error (2-sided)	5%	
Power	80%	~ 87%
Recruitment period	~ 53 months [3]	~ 23 months
Follow-up time after the last patient is randomised	~ 5 months	~3 5 months
Assumed drop-out rate	10%	
Number of primary endpoint (OS) events	247 [4]	[~ 297] [4]
Duration until primary OS analysis	~ 58 months [4]	
Number of patients	~ 330	~ *382*
Total sample size in the study	~ 572 patients (382 all-comers plus ~ 190 additional PD-L1-positive patients)	

Abbreviations: CCO=clinical cut-off; HR=hazard ratio; mITT=modified Intent-to-Treat; OS=Overall Survival; PD-L1=Programmed death-ligand 1

[1] The PD-L1-positive population includes all patients randomised in the study (before and after protocol version 4.0) whose PD-L1 status was IC1/2/3 at the time of randomisation.

[2] The mITT population includes all patients randomised in the study before protocol version 4.0 (PD-L1-positive and PD-L1-negative).

[3] Including the 23-month recruitment period for all-comers.

[4] The CCO date for the primary endpoint analysis will take place when the required number of 247 mortality events have been reported in the PD-L1-positive population (projected to occur approximately 58 months after FPI). By this time-point, approximately 297 mortality events are expected to have occurred in the mITT population under the study clinical assumptions.

Note: Calculations were conducted in R version 1.9.1

6.1.1 China Population

After approximately 572 patients have been randomised in the Global study, global recruitment will be closed. Additional patients with PD-L1-positive tumour status may be subsequently randomised in China only, following the same randomisation procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1 positive tumour status in mainland China (including patients enrolled in the Global study). The sample size of the China population was determined by characterizing the efficacy and safety profile of atezolizumab combined with chemotherapy.

Refer to Section 6.11 and the SAP for further details.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enrol, discontinue, or complete the study will be summarised. Reasons for premature study withdrawal will be listed and summarised.

6.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables such as age, sex, race/ethnicity, stratification variables and other relevant baseline characteristics will be summarised using means, standard deviations (SDs), medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.4 EFFICACY ANALYSES

Efficacy analyses will be performed separately for the PD-L1 positive and mITT populations. Further details will be provided in the SAP.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study, OS, is defined as the time from randomisation to death from any cause.

In order to control for the overall type I error at two-sided 5%, OS will be evaluated hierarchically in the following fixed order:

(1) OS in the PD-L1-positive population (based on all patients randomised in the study whose PD-L1 status was IC1/2/3 at the time of randomisation),

(2) OS in the mITT population (based on all patients randomised in the study before protocol version 4.0),

with patients grouped according to their treatment assigned at randomisation.

A confirmatory test on (2) will only be conducted if the null-hypothesis for (1) has been rejected at a two-sided 5% significance level.

Patients without a reported death event at the time of the analysis will be censored on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomisation +1 day.

OS will be compared between treatment arms using the stratified log-rank test, based on the stratification factors provided at randomisation (as documented in the IxRS): presence of visceral (lung and/or liver) metastases (yes vs. no), tumour PD-L1 status (tumour-infiltrating immune cell [IC]0 vs. IC1/2/3) and chemotherapy choice (carboplatin/gemcitabine vs. capecitabine). For OS in the PD-L1-positive population, presence of visceral metastases and chemotherapy choice will be used as stratification factors. The hazard ratio (HR) for death will be estimated using a stratified Cox regression model, using the same stratification factors as used for the log-rank test; HR estimate for treatment effect (addition of atezolizumab to chemotherapy vs. chemotherapy alone) and corresponding two-sided 95% CI will be provided.

Results from an unstratified analysis will also be provided as a sensitivity analysis.

Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

Sensitivity analysis of OS may also be completed based on the FAS population (i.e., in all patients randomised in the study, before and after protocol version 4.0), with the ''stage'' of study (before and after protocol version 4.0) used as an additional stratification factor. Further details will be provided in the SAP (as applicable).

The CCO date for the primary endpoint analysis will take place when the required number of 247 mortality events have been reported in the PD-L1-positive population. This is expected to occur approximately 58 months after FPI. By this time-point, approximately 297 mortality events are expected to have occurred in the mITT population.

Further details will be specified in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- 12-month survival rate;
- 18-month survival rate;
- PFS;
- ORR, by investigator assessment using RECIST v1.1 (see Appendix 3), in the ORR-evaluable population;
- DoR, by investigator assessment using RECIST v1.1 (see Appendix 3), in the DoR-evaluable population;
- CBR, by investigator assessment using RECIST v1.1 (see Appendix 3), in the ORR-evaluable population;
- Time to confirmed deterioration (TTD) in GHS/QoL (Items 29, 30 of the EORTC QLQ-C30), *in the PD-L1(SP142)-positive population and the mITT population*

In addition, confirmed ORR and confirmed DoR will be analysed. Further details will be provided in the SAP.

6.4.2.1 12-month and 18-month Survival

The 12-month survival rate is defined as the proportion of patients alive 12 months after randomisation, and 18-month survival rate is defined as the proportion of patients alive 18 months after randomisation. The 12-month and 18-month survival rates will be estimated by Kaplan-Meier methodology for each treatment arm and the 95% CI will be calculated using Greenwood's formula (Greenwood 1926). The 95% CIs for the difference in OS rates between the two arms will be estimated using the normal approximation method.

6.4.2.2 Progression-free Survival

PFS is defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator from tumour assessments using RECIST v1.1 (see Appendix 3), or death from any cause during the study, whichever occurs first.

Analysis of PFS will be completed using the same methods as described for the primary endpoint (OS).

Data for patients who have not experienced disease progression or death will be censored at the last tumour assessment date. If no tumour assessment was performed after randomisation, data will be censored at the date of randomisation +1 day.

6.4.2.3 Objective Response Rate

An objective response is defined for patients with measurable disease at baseline who achieved a documented unconfirmed response [i.e., either a partial response (PR) or a complete response (CR)] on the basis of investigator assessment using RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumour assessment, will be considered as non-responders. Objective response rate is defined as the proportion of patients who have an objective response. ORR will be analysed in the Response-evaluable population.

An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method.

The ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint of OS. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

Confirmation of response was not required at the initiation of the study. Confirmed ORR will be derived as per details provided in the SAP.

6.4.2.4 Duration of Objective Response

DoR is defined as the time from the first occurrence of a documented unconfirmed response (CR or PR) until the date of disease progression per RECIST v1.1 or death from any cause, whichever occurs first. DoR is evaluated in the subset of patients with measurable disease at baseline, who have achieved an objective response (DoR-evaluable population).

Data for patients who have not experienced disease progression or death will be censored at the last tumour assessment date. If no tumour assessments were performed after the date of the first occurrence of CR or PR, data for DoR will be censored at the date of the first occurrence of CR or PR +1 day.

The analysis of DoR is based on a non-randomised subset of patients (those who achieved an unconfirmed response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes only. The methodologies described for the analysis of PFS will be used for the analysis of DoR, except that the analysis will not be stratified.

Confirmation of response was not required at the initiation of the study. Confirmed DoR will be derived as per details provided in the SAP.

6.4.2.5 Clinical Benefit Rate

Clinical benefit rate (CBR), defined as the percentage of patients who have achieved either unconfirmed CR, unconfirmed PR, or stable disease (SD) that lasts at least 6 months. CBR will be compared between the two treatment arms.

6.4.2.6 Time to Confirmed Deterioration in Global Health Status/Health-Related Quality of Life

The primary patient-reported endpoint is the TTD in GHS/QoL. Deterioration in GHS/QoL (Items 29, 30 of the EORTC QLQ C30) is defined by the following two criteria:

1. The time from randomisation to the first time the patient's GHS/QoL scale score shows a ≥10-point decrease from the baseline scale score. A 10-point change is defined as the minimally important difference (MID) (Osoba et al. 1998).
2. The decrease of ≥10-points from baseline score must be held for at least two consecutive cycles, or an initial decrease of ≥10-points from baseline score is followed by death or treatment discontinuation within 3 weeks from the last assessment.

PRO completion rates will be summarised at each timepoint by treatment arm. TTD in GHS/QoL will be compared between the treatment groups using the same method as the primary endpoint of OS. A subgroup analysis of TTD in GHS/QoL will also be conducted for each chemotherapy type subgroup (i.e., carboplatin/gemcitabine and capecitabine groups). Patients who have not deteriorated before the last PRO assessment is completed will be censored at this time-point.

In addition, the impact of non-protocol therapy on the PRO endpoint of TTD in GHS/QoL will be evaluated in patients that completed the PRO assessments. A sensitivity analysis will be performed in which data for patients who received NPT will be censored at the last PRO assessment date before receiving non-protocol treatment.

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Patient-Reported Outcomes of Function and Disease/Treatment-Related Symptoms - EORTC Data

Summary statistics (mean and 95% CIs, standard deviation, median, and range) and mean change from baseline with 95% CIs of linearly transformed absolute scores will be calculated for all function scales and symptom items/scales of the EORTC QLQ-C30 and QLQ-BR23 at each assessment timepoint for each arm. The mean change from baseline (and 95% CI) will be assessed on patients with at least one post-baseline measurement to further inform TTD in QoL and of patients' treatment experience. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and disease/treatment-related symptoms scales (Osoba et al. 1998; Cocks et al. 2011).

A longitudinal analysis will be conducted to estimate the effect difference on PRO repeated responses over a selected period of time and between the treatment arms, and mixed models on a set of covariates (baseline domain score, patient demographic, and clinical variables) will be conducted. Change from baseline at subsequent cycles will be presented by treatment arm and will include least squares mean (LS Mean), difference in LS Mean between two treatment arms, and 95% CIs for the differences. The standard error (SE) will also be calculated for each LS Mean.

The EORTC QLQ-C30 and QLQ-BR23 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). Missing data will be assessed and reported by cycle. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals

and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing. PRO completion, compliance rates, and reasons for missing data will be summarised at each timepoint by treatment arm.

6.4.3.2 FACT-G, GP5 Single Item Data

A descriptive analysis of absolute scores and the number and proportion of patients selecting each response option at each assessment time-point by treatment arm will be reported for item GP5 ("I am bothered by side effects of treatment") from the FACT-G physical well-being subscale. A *descriptive analysis of the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported using the PD-L1(SP142)-positive population and the mITT population. Additionally, the proportion of patients reporting improvement, deterioration or no change in symptoms following the first assessment will be provided.* Graphical representation of FACT G GP5 data over time will also be provided. Item GP5 from version 4 of the FACT-G questionnaire will be scored according to the FACIT scoring manual (Cella 1997) and PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

6.4.3.3 Health Economic EQ-5D-5L Data

Health economic data, as assessed by the EQ-5D-5L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-5L assessment. The results from the health economic data analysis will be reported separately from the clinical study report.

6.4.4 Controlling for Type I Error

All tests will be performed at two-sided alpha of 5% with testing for secondary endpoints conducted hierarchically, using a fixed sequence testing approach (Westfall and Krishen, 2001), where each subsequent hypothesis will be tested only if all previously tested hypotheses have been rejected, according to the following pre-specified and fixed order of endpoints:

Primary endpoint:

1. OS (PD-L1 positive population)
2. OS (mITT population)

Secondary endpoints:

1. PFS by RECIST v1.1 (PD-L1 positive population)
2. PFS by RECIST v1.1 (mITT population)
3. ORR by RECIST v1.1 (Response-evaluable subset of the PD-L1 positive population)
4. ORR by RECIST v1.1 (Response-evaluable subset of the mITT population).

The remaining secondary endpoints (12-month and 18-month OS rates, TTD in the GHS/QoL, PFS rate at 12 months, DoR, CBR, as well as C-ORR and C-DoR) will not be adjusted for multiple testing.

Further details or any updates to the testing strategy will be provided in the SAP.

6.4.5 Handling of Missing Data

Data for patients without a registered death event at the time of the OS analysis will be censored at their last study follow-up date, i.e. on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomisation +1 day.

For PFS, patients without a date of disease progression will be analysed as censored observations at the last tumour assessment date. If no post-baseline tumour assessment is available, data will be censored at the date of randomisation +1 day (see Section 6.4.2.2).

For objective response, patients without any post-baseline assessment will be considered non-responders.

Handling of missing PRO data is described in Section 6.4.2.6 and Section 6.4.3.1.

6.5 SAFETY ANALYSES

Safety analyses will include all randomised patients who received at least one dose of study treatment (atezolizumab/placebo or chemotherapy), with patients grouped according to the treatment actually received.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, study treatment exposures, and will be presented by treatment arm.

Verbatim descriptions of adverse events will be mapped to MedDRA terms. Treatment-emergent events will be summarised by MedDRA term, appropriate MedDRA levels (for example, system organ class [SOC] and preferred term [PT]), and NCI CTCAE v4.0 grade, regardless of relationship to study drug as assessed by the investigator. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will also be summarised:

- Adverse events assessed as related to the study drug;
- Adverse events leading to permanent discontinuation of study drug (with or without withdrawal from the study);
- Adverse events leading to dose reduction or interruption;
- Grade 3-4 adverse events;
- Grade 5 adverse events;
- Serious adverse events; and
- Adverse events of special interest.

All deaths and causes of deaths will be summarised.

Relevant laboratory values will be summarised, with NCI CTCAE Grade 3 and Grade 4 values identified, where appropriate. Changes in NCI CTCAE grade will be tabulated by treatment arm.

For details on immunogenicity analyses, as measured by ADA, refer to Section 6.7.

6.6 PHARMACOKINETIC ANALYSES

The PK analyses will include patients who received at least one dose of study treatment and provided at least one evaluable post-dose PK, with patients grouped according to treatment received.

Atezolizumab serum concentration data (C_{min} and C_{max}) will be measured at specific timepoints (see Appendix 2), tabulated and summarised. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK analyses may be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

To evaluate the immunogenicity of atezolizumab, the incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline will be analysed. The immunogenicity analyses will include patients with at least one predose and one postdose ADA assessment, with patients grouped according to treatment received.

Patients will be classified as ADA positive if they were ADA negative at baseline or missing data but developed an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titre of one or more post-baseline samples is at least 4-fold greater (i.e., ≥0.60 titre units) than the titre of the baseline sample (treatment-enhanced ADA response). Patients will be classified as ADA negative if they were ADA negative or missing data at baseline and all post-baseline samples are negative, or if they were ADA positive at baseline but do not have any post-baseline samples with a titre that is at least 4-fold greater than the titre of the baseline sample (treatment unaffected).

The numbers and proportions of ADA-positive patients and ADA-negative patients will be summarised by treatment arm and listed by patient and cycle.

Exploratory immunogenicity endpoints (relationships between ADA status and efficacy, safety, or pharmacokinetics endpoints) may be analysed and reported descriptively.

6.8 BIOMARKER ANALYSES

To evaluate the action of the drug combination (atezolizumab plus chemotherapy) according to prospectively determined PD-L1 expression, analyses of the relationship between PD-L1 status by immunohistochemistry (PD-L1-positive: IC1/2/3 vs PD-L1-negative: IC0), and clinical efficacy outcomes will be undertaken.

6.8.1 Exploratory Biomarker Analyses

To assess biomarkers that are predictive of response to atezolizumab (i.e., predictive biomarkers), are associated with outcomes independent of treatment (i.e., prognostic biomarkers), as well as pharmacodynamic exploratory biomarkers in tumour tissues (e.g. screening, on-treatment, and at disease progression sample) and blood and their association with disease status and/or response to study drug, the following exploratory biomarker analyses may be undertaken:

- Relationship between tumour immune-related or disease type-related biomarkers (including but not limited to TILs and CD8) by immunohistochemistry in tumour tissues, and clinical outcomes;
- Relationship between PD-L1 status measured by various immunohistochemistry assays and clinical outcomes;
- Relationship between certain molecular subgroups and pre-defined gene signatures by RNA expression analysis in tumour tissues, and clinical outcomes;
- Relationship between DNA mutations and mutational burden assessed in tumour tissue, and clinical outcomes;
- Relationship between exploratory biomarkers (including but not limited to circulating cell-free DNA, proteins and cytokines) in plasma collected before treatment, during treatment and at disease progressions, and clinical outcomes;
- Changes in blood- and tissue- based biomarkers under chemotherapy+/- atezolizumab treatment in relation to clinical outcomes.
- Correlation of immune biomarker findings in blood and tissue samples from this study to findings from other studies in TNBC and other tumour types.

With the exception of PD-L1 data (stratification factor), results of biomarker analyses will not be included in the Clinical Study Report.

Patients enrolled in mainland China will only be included in exploratory biomarker analyses that are based on mandatory tumour tissue samples collected at screening.

6.9 SUBGROUP ANALYSES

To assess the consistency of treatment benefit in subgroups, OS and PFS will be evaluated by demographic and relevant baseline characteristics. Further details will be provided in the SAP.

Consistency of treatment benefit will be assessed using unstratified Cox Proportional hazards models, and hazard ratios with 95% CIs will be estimated. Forest plots will be used to summarize the results.

6.10 INTERIM ANALYSIS

6.10.1 Planned Interim Analysis

No interim analyses of efficacy are planned. The iDMC will review safety data periodically during the study. Any outcomes from these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards and/or Ethics Committees.

6.10.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an interim efficacy analysis, e.g., based on a recommendation from the iDMC and in consultation with the Steering Committee. If an interim analysis is conducted, it will be prospectively described in the SAP, and the Sponsor will remain blinded.

Provisions will be in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, which will be submitted to relevant health authorities at least two months prior to the conduct of the interim analysis. In addition, the iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor based on the results of the analysis. The iDMC charter will also be made available to relevant health authorities.

6.11 CHINA POPULATION ANALYSES

The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in the China population (enrolled in the Global study and during additional recruitment in China) is consistent with the efficacy observed in the global population (Global study). Therefore, no formal hypothesis testing will be performed for China population.

The final analysis of OS in the China population will be conducted *when approximately 49 deaths in the China population have been observed. Assuming a hazard ratio of 0.7 for OS in the global population, the 49 OS events will provide approximately 75% probability of maintaining 50% of risk reduction compared to that estimated in the global population. The CCOD of OS analysis in the China population may be revisited according to the data maturity and estimated treatment effect from the global population.*

Analyses of study conduct and treatment group comparability (including demographic and baseline disease characteristics) will be performed similarly as described in Sections 6.2 and 6.3, respectively.

Analysis of the efficacy endpoints for the China population will be performed in a similar way as described for the Global population in Sections 6.4.1 and 6.4.2 when appropriate, except that unstratified instead of stratified analysis will be performed. This is due to the consideration of the limited sample size of the China population, and small strata cell representation.

Safety data for the China population will be analysed using the same methods as described in Section 6.5.

Results from these analyses will be summarised in a separate report from the clinical study report (CSR) for the Global study.

Further details will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The global Contract Research Organisation (CRO) will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the CRO.

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

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERISED SYSTEMS

When clinical observations are entered directly into a study 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study 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. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws*. Studies conducted in China will be in accordance with the approved local Informed Consent Form and applicable laws and will comply with the approved HGRAC main and exploratory applications (when applicable).

8.2 INFORMED CONSENT

The Sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs, or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the ICF will contain separate sections for any optional procedures. The investigator or authorised designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms, or the addendum, according to the applicable local law and IRB/EC policy. Patients who are in the post-treatment survival follow-up or their legally authorized representatives will be informed of revisions to the Consent Forms via phone call and these notifications will be recorded in the respective patient charts. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process, and that written informed consent was obtained using the updated/revised Consent Forms, as required by local laws and IRB/EC policy for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

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

9.2 PROTOCOL DEVIATIONS

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

The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorised representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann La Roche Ltd.

A total of approximately 572 patients will be randomised at around 135 sites globally (in select countries from Europe, Asia/Pacific, as well as North-, and South America) over approximately 53 months. This total accounts for an estimated 10% drop-out rate during the study. Patients will be randomised centrally, using an IxRS.

Total recruitment in China (to randomise approximately 70 patients with PD-L1-positive tumour status in the Global study and during additional enrolment in China combined) will be approximately 23 months.

Clinical operations, data management, day-to-day clinical science monitoring, and statistical programming responsibilities will be $partially$ outsourced.

Central testing laboratories will be responsible for the following:

- Confirmation of PD-L1 status of prospective study patients and retrospective confirmation of ER, PR, and HER2 triple negative status (as applicable)
- Biomarker assays (blood-based* and tumour sample-based)
- PK assays
- ADA assays.

*Patients enrolled in mainland China will not undergo plasma and whole blood sample collection for biomarker assays.

Supply kits for all central laboratory assessments will be provided, and PD-L1 (prospective testing), HER2, ER, and PR prospective testing or retrospective confirmation) will be completed by designated central laboratories.

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Clinical data will be captured using standard eCRFs, the design of which will be consistent with the eCRFs of other atezolizumab clinical trials.

There will be one SAP for the Global study and for the China population. However, separate CSRs will be prepared for the Global study, and for the China population.

Responsibilities of the study SC and the iDMC will be provided in the respective committee charters.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and*/or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

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

Adams S, Diamond J, Hamilton E, et al. Safety and clinical activity of atezolizumab (anti-PDL1) in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer [abstract]. In: Proceedings of the Thirty-Eighth Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2015 Dec 8-12; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2016;76(4 Suppl):Abstract Nr P2-11-06. DOI: 10.1158/1538-7445.SABCS15-P2-11-06.

Adams S, Diamond J, Hamilton E, et al. Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). J Clin Oncol 34, 2016 (suppl; abstr 1009).

Adams S, Gray R, Demaria S, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol 2014;32:2959−66.

Adams S, Loi S, Toppmeyer D et al. Phase 2 study of pembrolizumab as first-line therapy for PD-L1–positive metastatic triple-negative breast cancer (mTNBC): Preliminary data from KEYNOTE-086 cohort B. J Clin Oncol 35, 2017b (suppl; abstr 1088). Presented at ASCO Annual Meeting on June 4, 2017.

Adams S, Schmid P, Rugo HS et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. J Clin Oncol 35, 2017a (suppl; abstr 1008). Presented at ASCO Annual Meeting on June 3, 2017.

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti-programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502-4.

Alba E, Chacon JI, Lluch A, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012;136:487–93. http://dx.doi.org/10.1007/s10549-012-2100-y.

Ali HR, Provenzano E, Dawson SJ, et al. Association between CD8+ T-cell infiltration and breast cancer survival in 12,439 patients. Ann Oncol. 2014 Aug;25(8):1536-43. doi: 10.1093/annonc/mdu191.

Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med. 2020 Jan 13. doi: 10.5858/arpa.2019-0904-SA.

Atezolizumab (TECENTRIQ; RO5541267) Investigator's Brochure. F. Hoffmann-La Roche Ltd. Version 17, September 2020.

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

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

Brookmeyer R, Crowley J. A K-sample median test for censored data. Journal of the American Statistical Association. 1982;77:433–440.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.

Brouckaert O, Wildiers H, Floris G, Neven P. Update on triple-negative breast cancer: prognosis and management strategies. Int J Womens Health. 2012;4:511-20. doi: 10.2147/IJWH.S18541.

Brufsky AM, Hurvitz S, Perez E, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2011 Nov 10;29(32):4286-93. doi: 10.1200/JCO.2010.34.1255.

Brufsky A, Valero V, Tiangco B, et al. Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Breast Cancer Res Treat. 2012 Jun;133(3):1067-75. doi: 10.1007/s10549-012-2008-6.

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

Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†. Ann Oncol. 2014 Oct;25(10):1871-88. doi: 10.1093/annonc/mdu385.

Cardoso F, Harbeck N, Fallowfield L, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2012;23 (Supplement 7):vii11−vii19.

Carey LA, Rugo HS, Marcom PK et al. TBCRC 001: randomized phase II study of cetuximab in combination with carboplatin in stage IV triple-negative breast cancer. J Clin Oncol. 2012;30:2615-23.

Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. J Clin Oncol 1993; 11:570-79.

Cella D. Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Version 4. Evanston: Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University, 1997.

Chen DS, Irving BA, Hodi FS, et al. Molecular pathways: next-generation immunotherapy–inhibiting programmed death−ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580−7.

Chen D and Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1-10.

Cimino-Mathews A, Ye X, Meeker A, et al. Metastatic triple-negative breast cancers at first relapse have fewer tumor-infiltrating lymphocytes than their matched primary breast tumors: a pilot study. Hum Pathol 2013;44:2055−63.

Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol. 2011 Jan 1;29(1):89-96. doi: 10.1200/JCO.2010.28.0107.

Cohen MH, Johnson JR, Chen YF, et al. FDA drug approval summary: erlotinib (Tarceva) tablets. Oncologist. 2005 Aug;10(7):461-6.

Collignon J, Lousberg L, Schroeder H, Jerusalem G. Triple-negative breast cancer: treatment challenges and solutions. Breast Cancer (Dove Med Press). 2016 May 20;8:93-107. doi: 10.2147/BCTT.S69488.

Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020 Dec 5;396(10265):1817-1828. doi: 10.1016/S0140-6736(20)32531-9.

Danforth DN Jr. Disparities in breast cancer outcomes between Caucasian and African American women: a model for describing the relationship of biological and nonbiological factors [serial online]. Breast Cancer Res. 2013;15:208.

den Brok WD, Speers CH, Gondara L et al. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. Breast Cancer Res Treat. 2017 Feb;161(3):549-556. doi: 10.1007/s10549-016-4080-9.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593-603. doi: 10.1080/19420862.2015.1136043.

Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti−CTLA-4 antibodies across clinical indications. Semin Oncol 2010;37:499−507.

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

Emens L, Braiteh F, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer (TNBC). [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR; Cancer Res 2015;75(15 Suppl):Abstract Nr 2859. doi:10.1158/1538-7445.AM2015-2859.

Emens LA, Adams S, Barrios CH, et al. IMpassion130: Final OS analysis from the pivotal phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325.

Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. Annals of Oncology 2021;32:983–993.

Emens LA, Molinero L, Loi S, et al. Atezolizumab and nab-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study. J Natl Cancer Inst. 2021 Aug 2;113(8):1005-1016. doi: 10.1093/jnci/djab004.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.

Fan Y, Xu BH, Yuan P, et al. Docetaxel-cisplatin might be superior to docetaxel-capecitabine in the first-line treatment of metastatic triple-negative breast cancer. Ann Oncol. 2013 May;24(5):1219-25. doi: 10.1093/annonc/mds603.

Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer. 2001 Jul;37(11):1331-4.

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

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 09/09/2016.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86. doi: 10.1002/ijc.29210.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485-99.

Fukada I, Araki K, Kobayashi K, et al. Therapeutic effect of taxanes on metastatic breast cancer of various immunohistochemical subtypes. Oncol Lett. 2016 Jul;12(1):663-669.

Gerratana L, Fanotto V, Pelizzari G, et al. Do platinum salts fit all triple negative breast cancers? Cancer Treat Rev. 2016 Jul;48:34-41. doi: 10.1016/j.ctrv.2016.06.004.

Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol. 2009;20(8):1319–1329.

González-Rivera M, Lobo M, López-Tarruella S, et al. Frequency of germline DNA genetic findings in an unselected prospective cohort of triple-negative breast cancer patients participating in a platinum-based neoadjuvant chemotherapy trial. Breast Cancer Res Treat. 2016 Apr;156(3):507-15. doi: 10.1007/s10549-016-3792-1.

Greene J, Hennessey B. The role of anthracyclines in the treatment of early breast cancer. J Oncol Pharm Pract. 2015 Jun;21(3):201-12. doi: 10.1177/1078155214531513.

Greenwood M. A report on the natural duration of cancer. Reports on Public Health and Medical Subjects. 1926;33:1-26. H.M. Stationary Office, London.

Gucalp A, Traina TA. Triple-negative breast cancer: adjuvant therapeutic options. Chemother Res Pract. 2011;2011:696208.

Hammond ME, Hayes DF, Wolff AC et al. American Society of Clinical Oncology/College of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract. 2010 Jul;6(4):195-7. doi: 10.1200/JOP.777003.

Hejblum G, Lambotte O, Galicier L, et al. A web-based Delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS ONE 2014;9(4):e94024. doi: 10.1371/journal.pone.0094024.

Herbst RS, Soria JC, Kowanetz M. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528):563-7. doi: 10.1038/nature14011.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ 5D-5L). Qual Life Res 2011;20:1727-36.

Hernandez-Aya LF, Ma CX. Chemotherapy principles of managing stage IV breast cancer in the United States. Chin Clin Oncol. 2016 Jun;5(3):42. doi: 10.21037/cco.2016.04.01.

Hirshfield KM, Ganesan S. Triple-negative breast cancer: molecular subtypes and targeted therapy. Curr Opin Obstet Gynecol. 2014 Feb;26(1):34-40. doi: 10.1097/GCO.0000000000000038.

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

Hudis CA, Gianni L. Triple-negative breast cancer: an unmet medical need. Oncologist. 2011;16 Suppl 1:1-11. doi: 10.1634/theoncologist.2011-S1-01.

Isakoff SJ, Mayer EL, He L, et al. TBCRC009: a multicenter phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. J Clin Oncol. 2015;33(17):1902-9.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ 5D 3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717-27.

Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. J Natl Cancer Inst. 2017 Sep 1;109(9). doi: 10.1093/jnci/djx030.

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

Kassam F, Enright K, Dent R, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer. 2009 Feb;9(1):29-33. doi: 10.3816/CBC.2009.n.005.

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

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immuno Methods 2008;333:1-9.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659–663.

Larkins E, Scepura B, Blumenthal GM, et al. U.S. Food and Drug Administration Approval Summary: Ramucirumab for the Treatment of Metastatic Non-Small Cell Lung Cancer Following Disease Progression On or After Platinum-Based Chemotherapy. Oncologist. 2015 Nov;20(11):1320-5. doi: 10.1634/theoncologist.2015-0221.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.

Lehmann B, Bauer J, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011;121:2750-67.

Leonard R, Hennessy BT, Blum JL, O'Shaughnessy J. Dose-adjusting capecitabine minimizes adverse effects while maintaining efficacy: a retrospective review of capecitabine for metastatic breast cancer. Clin Breast Cancer. 2011 Dec;11(6):349-56. doi: 10.1016/j.clbc.2011.06.005.

Li Q, Li Q, Zhang P, et al. A phase II study of capecitabine plus cisplatin in metastatic triple-negative breast cancer patients pretreated with anthracyclines and taxanes. Cancer Biol Ther. 2015;16(12):1746-53. doi: 10.1080/15384047.2015.1095400.

Li X, Yang J, Peng L, et al. Triple-negative breast cancer has worse overall survival and cause-specific survival than non-triple-negative breast cancer. Breast Cancer Res Treat. 2017 Jan;161(2):279-287. doi: 10.1007/s10549-016-4059-6.

Liang X, Di L, Song G, et al. Capecitabine maintenance therapy for XT chemotherapy-sensitive patients with metastatic triple-negative breast cancer. Chin J Cancer Res. 2014 Oct;26(5):550-7. doi: 10.3978/j.issn.1000-9604.2014.10.02.

Liao Y, Fan Y, Wan Y, Li J, Peng L. Acceptable but limited efficacy of capecitabine-based doublets in the first-line treatment of metastatic triple-negative breast cancer: a pilot study. Chemotherapy. 2013;59(3):207-13. doi: 10.1159/000356156

Lin NU, Vanderplas A, Hughes ME, et al. Clinico-pathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012;118:5463.

Loi S. Host antitumor immunity plays a role in the survival of patients with newly diagnosed triple-negative breast cancer. J Clin Oncol 2014;32:2935−7.

Loi S, Michiels S, Salgado R, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol 2014;25:1544-50.

Lund MJ, Trivers KF, Porter PL, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat 2009, 113:357-370.

Lundqvist A, Andersson E, Ahlberg I, et al. Socioeconomic inequalities in breast cancer incidence and mortality in Europe-a systematic review and meta-analysis. Eur J Public Health. Eur J Public Health. 2016 Oct;26(5):804-813.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355-62.

Mersin H, Yildirim E, Berberoglu U, Gülben K. The prognostic importance of triple negative breast carcinoma. Breast. 2008;17(4):341–346.

Michalaki V, Karvouni E, Dafnios N, et al. Phase 2 study of eribulin mesylate in combination with carboplatin in patients with advanced triple-negative breast cancer. J Clin Oncol 34, 2016 (suppl; abstr e12551) DOI: 10.1200/JCO.2016.34.15_suppl.e12551

Miles DW, Gligorov J, Andre F, et al. Primary results from IMpassion131, a double-blind placebo-controlled randomised phase III trial of first-line paclitaxel (PAC) ± atezolizumab (atezo) for unresectable locally advanced/metastatic triple-negative breast cancer (mTNBC). Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325.

Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. Ann Oncol. 2021;32:994–1004.

Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016 Jul;66(4):271-89. doi: 10.3322/caac.21349.

Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008;109:123–139.

Nanda R, Chow L, Dees E, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib Keynote-012 Study. J Clin Oncol 2016 Jul 20;34(21):2460-7. doi: 10.1200/JCO.2015.64.8931.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2. April 26, 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf. Last accessed on June 9, 2017.

Nigenda G, Gonzalez-Robledo MC, Gonzalez-Robledo LM, Bejarano-Arias RM. Breast cancer policy in Latin America: account of achievements and challenges in five countries. Global Health. 2016 Jul 12;12(1):39. doi: 10.1186/s12992-016-0177-5.

[No authors listed]. Immunotherapy Slows TNBC Progression. Cancer Discov. 2015 Jun;5(6):570. doi: 10.1158/2159-8290.CD-NB2015-059.

O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med. 2011;364(3):205–14.

O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. J Clin Oncol. 2014;32(34):3840–7. doi: 10.1200/JCO.2014.55.2984.

Osoba D, Aaronson N, Zee B, et al. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. Qual Life Res 1997;6:103-8.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality of life score. J Clin Oncol 1998;16:139-44.

Penault-Llorca F, Viale G. Pathological and molecular diagnosis of triple-negative breast cancer: a clinical perspective. Ann Oncol. 2012 Aug;23 Suppl 6:vi19-22.

Petrelli F, Barni S, Bregni G, de Braud F, Di Cosimo S. Platinum salts in advanced breast cancer: a systematic review and meta-analysis of randomized clinical trials. Breast Cancer Res Treat. 2016 Dec;160(3):425-437.

Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol. 2008 Apr 20;26(12):1980-6. doi: 10.1200/JCO.2007.10.8399.

Pivot XB, Li RK, Thomas ES, et al. Activity of ixabepilone in oestrogen receptor-negative and oestrogen receptor-progesterone receptor-human epidermal growth factor receptor 2-negative metastatic breast cancer. Eur J Cancer 2009;45:2940-6. DOI: 10.1016/j.ejca.2009.07.015

Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515:558-62.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481-9

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323-35.

Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011 Apr 1;29(10):1252-60. doi: 10.1200/JCO.2010.28.0982.

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

Rosenberg AS, Worobec AS. A risk-based approach to immunogenicity concerns of therapeutic protein products. BioPharm Intl 2004;17:34-42.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Rugo HS, Cortes DW, Cescon S, et al. LBA16-KEYNOTE-355: Final results from a randomized, double-blind phase III study of first-line pembrolizumab + chemotherapy vs placebo + chemotherapy for metastatic TNBC. Annals of Oncology [abstract on the internet] Sept 2021 [cited 28 October 2021];32 (suppl_5):S1283-S1346. 10.1016/annonc/annonc741. Available from: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/keynote-355-final-results-from-a-randomized-double-blind-phase-iii-study-of-first-line-pembrolizumab-chemotherapy-vs-placebo-chemotherapy-for.

Saha P, Nanda R. Concepts and targets in triple-negative breast cancer: recent results and clinical implications. Ther Adv Med Oncol. 2016 Sep;8(5):351-9. doi: 10.1177/1758834016657071.

Schmid P, Adams S, Hope S. Rugo HS, et al. IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC). J Clin Oncol. 37, no. 15_suppl (May 20, 2019) 1003-1003. DOI: 10.1200/JCO.2019.37.15_suppl.1003

Schmid P, Adams S, Rugo HS, et al; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121. doi: 10.1056/NEJMoa1809615.

Schmid P, Cruz C, Braiteh FS, et al. Atezolizumab in metastatic triple-negative breast cancer: long-term clinical outcomes and biomarker analyses. Abstract presented at: AACR Annual Meeting 2017; April 1-5, 2017; Washington DC. Abstract 2986.

Schmid P, Rugo HS, Adams S, et al; Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jan;21(1):44-59. doi: 10.1016/S1470-2045(19)30689-8.

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30. doi: 10.3322/caac.21387.

Sikov WM, Berry DA, Perou CM, Singh B, Cirrincione CT, Tolaney SM, et al. Impact of the Addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33:13–21. http://dx.doi.org/10.1200/JCO.2014.57.0572.

Skrypnikova M, Frolova M, Ignatova E, Pokataev I, Stenina M, Tjulandin S. Primary systemic therapy with metronomic doxorubicin, cyclophosphamide, and capecitabine in locally advanced and metastatic triple-negative breast cancer. J Clin Oncol 2011; 29:1110.

Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756-68.

Summers J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab plus interferon for advanced renal cell carcinoma. Oncologist. 2010;15(1):104-11. doi: 10.1634/theoncologist.2009-0250.

Tassone P, Di Martino MT, Ventura M, et al. Loss of BRCA1 function increases the antitumor activity of cisplatin against human breast cancer xenografts in vivo. Cancer Biol Ther. 2009;8(7):648–53.

Telli ML, Jensen KC, Vinayak S, et al. Phase II Study of Gemcitabine, Carboplatin, and Iniparib as Neoadjuvant Therapy for Triple-Negative and BRCA1/2 Mutation-Associated Breast Cancer with Assessment of a Tumor-Based Measure of Genomic Instability: PrECOG 0105. Journal of Clinical Oncology. 2015 April 6. pii: JCO.2014.57.0085.

The Cancer Genome Atlas Network (TCGAN). Comprehensive molecular portraits of human breast tumours. Nature 04 October 2012;490:61–70. doi:10.1038/nature11412 Available at: http://www.nature.com/nature/journal/v490/n7418/full/nature11412.html. Accessed on November 23, 2016.

Tommiska J, Bartkova J, Heinonen M, et al. The DNA damage signalling kinase ATM is aberrantly reduced or lost in BRCA1/BRCA2-deficient and ER/PR/ERBB2-triple-negative breast cancer. Oncogene. 2008;27(17):2501-6.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.

Turner NC, Tutt AN. Platinum chemotherapy for BRCA1-related breast cancer: Do we need more evidence? Breast Cancer Res 2012;14:115.

Tutt A, Ellis P, Kilburn L, Gilett C, Pinder S, Abraham J, et al. TNT: a randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). San Antonio, TX: Presented at: 37th Annual San Antonio Breast Cancer Symposium; 2014. p. 9–13 [abstract S3-01].

Trivers KF, Lund MJ, Porter PL, et al. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control. 2009 Sep;20(7):1071-82. doi: 10.1007/s10552-009-9331-1.

Verma S, Provencher L, Dent R. Emerging trends in the treatment of triple-negative breast cancer in Canada: a survey. Curr Oncol. 2011 Aug;18(4):180-90.

von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014;15:747–56. http://dx.doi.org/10.1016/S1470-2045(14)70160-3.

Wahba HA, El-Hadaad HA. Current approaches in treatment of triple-negative breast cancer. Cancer Biol Med. 2015 Jun;12(2):106-16. doi: 10.7497/j.issn.2095-3941.2015.0030.

Wang Y, Waters J, Leung M, et al. Clonal evolution in breast cancer revealed by single nucleus genome sequencing. Nature 2014;512:155-60.

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference 2001; 99:25–41.

Wolff AC, Hammond ME, Allison KH, et al; American Society of Clinical Oncology; College of American Pathologists. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018 Jul 10;36(20):2105-2122. doi: 10.1200/JCO.2018.77.8738.

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

Yardley DA, Brufsky A, Coleman RE, et al. Phase II/III weekly nab-paclitaxel plus gemcitabine or carboplatin versus gemcitabine/carboplatin as first-line treatment of patients with metastatic triple-negative breast cancer (the tnAcity study): study protocol for a randomized controlled trial. Trials. 2015 Dec 16;16:575. doi: 10.1186/s13063-015-1101-7.

Yardley D et al. nab-Paclitaxel + Carboplatin or Gemcitabine vs Gemcitabine + Carboplatin as First-Line Treatment for Patients with Triple-Negative Metastatic Breast Cancer: Results from the Randomized Phase II Portion of the tnAcity Trial. Poster 874. Presented at the 2016 San Antonio Breast Cancer Symposium (SABCS), December 6-10, 2016.

Yardley DA, Ward PJ, Daniel BR, et al. Panitumumab, Gemcitabine, and Carboplatin as Treatment for Women With Metastatic Triple-Negative Breast Cancer: A Sarah Cannon Research Institute Phase II Trial. Clin Breast Cancer. 2016 Oct;16(5):349-355. doi: 10.1016/j.clbc.2016.05.006.

Yoshimoto M, Takao S, Hirata M, et al. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. Cancer Chemother Pharmacol. 2012 Aug;70(2):331-8. doi: 10.1007/s00280-012-1826-x.

Zeichner SB, Ambros T, Zaravinos J, et al. Defining the survival benchmark for breast cancer patients with systemic relapse. Breast Cancer (Auckl). 2015a;9:9–17.

Zeichner SB, Herna S, Mani A, et al. Survival of patients with de-novo metastatic breast cancer: analysis of data from a large breast cancer-specific private practice, a university-based cancer center and review of the literature. Breast Cancer Res Treat. 2015b;153(3):617–624.

Zeichner SB, Terawaki H, Gogineni K. A Review of Systemic Treatment in Metastatic Triple-Negative Breast Cancer. Breast Cancer (Auckl). 2016 Mar 22;10:25-36. doi: 10.4137/BCBCR.S32783.

Zitvogel L, Apetoh L, Ghiringhelli F et al. The anticancer immune response: indispensable for therapeutic success? J Clin Invest 2008;118:1991−2001.

APPENDICES

APPENDIX 1 SCHEDULE OF ACTIVITIES

Assessment Day (Window)	Screening	All Cycles		Treatment Discontinuation Visit*	Follow-Up Every 3 months (± 21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a1]	30 (±5) Days after Last Dose	
Written informed consent [b]	x				
Demographics and medical histories [c]	x				
HIV, HBV and HCV serology [d]	x				
Physical examination [e] [f]	x	x		x	
ECOG performance status [f]	x	x		x	
Vital signs [g]	x	x	x	x	
Weight	x	x		x	
Height	x				
12-lead electrocardiogram [h]	x	As clinically indicated			
Head CT or MRI	x				
Tumour assessments [i]	x	Until disease progression only: q8w for first 12 months, q12w thereafter			
EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L [j]		x		x	x [k]
FACT-G (GP5 only) [j]		Beginning at Cycle 2		x	x [k]
Haematology and serum chemistry [l] [f]	x [m]	x	x	x	

Assessment Day (Window)	Screening	All Cycles		Treatment Discontinuation Visit*	Follow-Up Every 3 months (± 21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a1]	30 (±5) Days after Last Dose	
Coagulation panel (aPTT, INR) [a]	x [m]	x		x	
Urinalysis [n]	x	Cycle 3 and thereafter as clinically indicated		x	
Pregnancy test [o] women of child-bearing potential only	x [m]	x		x	
TSH, free T3, free T4 [p]	x	Cycle 1 and every fourth cycle thereafter		x	
Mandatory FFPE tumour tissue sample [q] [r]	x				
Optional FFPE tumour tissue samples [s] [r]		Cycle 2 only		At disease progression	
Whole blood sample for germline DNA analysis [t] [r]		Cycle 1 only			
Mandatory plasma sample for biomarker analysis [r]		Cycles 1 - 3 only, then every 3 months		At disease progression	
ADA sample collection [u] [r]		Cycles 1 - 4 only		x	
Serum atezolizumab PK sample collections [r]		Cycles 1 - 4 only		x	
Concomitant medications [v]	x	x	x	x	
Adverse events [w]	x	x	x	x	x
Atezolizumab/placebo infusion [x]		x			
Carboplatin/gemcitabine administration [y]		x	x		

Assessment Day (Window)	Screening	All Cycles		Treatment Discontinuation Visit*	Follow-Up Every 3 months (± 21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a1]	30 (±5) Days after Last Dose	
applicable patients only					
Capecitabine administration [z] applicable patients only		Days 1 to 14 *[z]*			
Survival and anti-cancer therapy follow-up [aa]					x

aPTT: activated partial thromboplastin time; ADA: anti-drug antibody; CT: computerised tomography; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L: EuroQoL 5 Dimension; ER/PR: oestrogen/progesterone receptors; FACT-G: Functional Assessment of Cancer Therapy: General; FFPE: fixed formalin paraffin embedded; HBV: hepatitis B virus; HCV: hepatitis C virus; HER2: human epidermal growth factor receptor 2; MRI: magnetic resonance imaging; PD-L1:programmed death ligand 1; PK: pharmacokinetics; q8w: every 8 weeks; q12w: every 12 weeks; QLQ-BR23: EORTC Breast Cancer-Specific Module; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone.

*The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

a. Assessments scheduled on the day of study treatment administration of each cycle should be performed prior to study treatment infusion unless otherwise noted. Assessments may be performed on Day 1 ± 3 days of each treatment cycle after cycle 1, unless otherwise noted (see footnote “f”, “j”, and Appendix 2). Coagulation panel tests on Day 1 of each cycle only apply to patients receiving capecitabine.

    a1. Assessments on Day 8 (±1 day) of each cycle only apply to patients receiving carboplatin/gemcitabine. Patients receiving capecitabine treatment and patients who are no longer receiving carboplatin/gemcitabine treatment are not required to attend the Day 8 visit of each cycle.

b. Written informed consent is required before performing any study-specific screening test or procedure unless these have already been conducted as standard of care. Signing of the ICF can occur more than 28 days before initiation of study treatment. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomisation. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to initiation of study treatment (except where otherwise specified) may be used for screening assessments rather than repeating such tests. Patients who do not meet the criteria for participation in this study may qualify for an additional re-screening opportunity (for a total of 2 screenings per patient) at the investigator's discretion, as described in Section 3.1.

c. Demographics include age, gender, self-reported race/ethnicity (where allowed by local regulations). Medical history includes reproductive status, smoking history, prior surgeries and cancer history (stage, date of diagnosis, prior anti-cancer treatment).

d. All patients will be tested for HIV locally prior to the inclusion into the study; HIV-positive patients will be excluded from the clinical study. Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) should be collected during screening and tested locally. Quantitative HBV DNA must be collected prior to randomisation in patients who have negative serology for HBsAg and HBsAb and positive serology for HBcAb. See eligibility criteria for how to interpret HBV testing. All patients will be tested for HCV locally prior to inclusion into the study; Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

e. A complete physical examination must be conducted at screening and the treatment discontinuation visit. Symptom-driven physical examinations may be conducted during treatment and may be done ≤ 96 hours of Day 1 treatment, and as clinically indicated. Physical examinations will include a review of the main body organs and systems, with special attention to cardiovascular (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs), respiratory (e.g., shortness of breath, crackling), gastrointestinal (e.g., abdominal pain, digestive disorders) systems, and a neurological exam focusing on signs and symptoms potentially indicative of disorders such as myasthenia gravis, motor and sensory neuropathy, meningitis, and encephalitis.

f. ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

g. At all clinic visits where study treatment is administered, vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before and 30 (±10) minutes after each infusion (atezolizumab/placebo, as well as gemcitabine and carboplatin in applicable patients). Vital signs will also be determined every 15 (±5) minutes during the atezolizumab/placebo infusions if clinically indicated or if symptoms occurred during the previous infusion. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

h. Standard 12-lead ECG, taken after resting in a supine position for at least 10 minutes. Additional cardiovascular monitoring (such as ECG and/or echocardiography) may be considered during the patient's study participation, if clinically indicated by the appearance of symptoms or findings at regular vital sign checks or medical examinations suggestive of cardiovascular disease (e.g. abnormally low or irregular pulse, chest pain, tachycardia, swollen legs, shortness of breath, crackling) especially if these cannot be explained by thyroid or electrolyte abnormalities.

i. Tumour assessments will be performed every 8 weeks for the first 12 months following randomisation, and every 12 weeks thereafter, until PD, death, withdrawal of consent, or study termination by the Sponsor (whichever occurs first). All measurable and evaluable lesions should be assessed and documented at screening (baseline) and during the study in accordance with RECIST 1.1. Results must be reviewed by the investigator before dosing at the next cycle.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumour assessments according to the protocol-specified schedule until they experience disease progression, withdraw consent, or die, or until the study closes, whichever occurs first, even if they started another anti-cancer therapy after study treatment discontinuation.

j. EORTC QLQ-C30, QLQ-BR23, FACT-G (single item GP5 only), and EQ-5D-5L questionnaires must be completed by the patient at the investigational site, both during the treatment phase and follow-up period, at the start of the clinic visit (or within 3 days prior to the visit), before discussion of the patient's health state, lab results or health record, before administration of study treatment, and/or prior to the performance of any other study assessments that could bias patients' responses. Interview assessment by a member of the clinical staff will be allowed if the patient is not able to complete the measure on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. In case the treatment is delayed or omitted, the patient should repeat the PRO assessment at the next visit, corresponding to the treatment administration day.

k. Patients who complete or discontinue the study treatment phase for any reason will continue to complete the EORTC QLQ-C30, QLQ-BR23, FACT-G (single item GP5 only), and EQ-5D-5L questionnaires in-clinic during the follow-up period at the following timepoints: every 3 months (±21 days) for Year 1, every 6 months (± 21 days) for Years 2–3, and then annually (± 21 days) thereafter.

l. Haematology consists of RBC count, haemoglobin, haematocrit, WBC count with differential (if clinically indicated), and platelet count. Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate (if part of standard analysis), calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Magnesium and phosphorus should be collected at screening, and thereafter only if clinically indicated. Glucose levels in diabetic patients receiving capecitabine must be monitored regularly during study treatment in accordance with local standards. Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms suggestive of pancreatitis.

m. Specified screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

n. Urinalysis by dipstick method includes specific gravity, pH, glucose, protein, ketones, and blood. During treatment, urinalysis will be performed on Day 1 of Cycle 3 and thereafter as clinically indicated.

o. Serum pregnancy test for women of childbearing potential at screening/baseline (within 14 days before Cycle 1, Day 1); after randomisation, urine pregnancy tests will be performed at every cycle and at treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

q. Results of PD-L1 testing of this mandatory screening tumour sample must be obtained from the designated central laboratory prior to enrolment. ER, PR, and HER2 triple-negative tumour status may be assessed locally prior to screening according to the latest ASCO guidelines and confirmed retrospectively by the designated central laboratory. If a fresh tumor sample is not clinically feasible, either the diagnosis sample, the primary surgical resection sample, or the most recent FFPE tumour biopsy sample should be used. An FFPE block or at least 17 unstained slides should be provided. Fine-needle aspiration,

brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Retrieval of archival tumor sample can occur outside the 28-day screening period. The sample will be included in exploratory biomarker research.

r. Refer to Appendix 2 for further details on sample collection times.

s. On-treatment and PD tumour samples for biomarker analyses are optional. They must be collected within 14 days prior to treatment on Day 1 of Cycle 2 and at disease progression (+/- 7 days) only if deemed clinically feasible by the investigator. Patients enrolled in mainland China will not undergo optional tumour tissue collections (on-treatment or at disease progression).

t. Mandatory whole blood for germline DNA isolation will be collected during the Baseline visit (Cycle 1 Day 1). If this sample has not been collected during the Baseline visit, it can be collected at any of the following cycles. Patients enrolled in mainland China will not undergo whole blood sample collection for germline DNA isolation.

u. Blood samples must be collected prior to study treatment administration on Day 1 of Cycles 1 to 4.

v. Includes all prescription or over-the-counter medications taken from 7 days prior to screening to the treatment discontinuation visit.

w. After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab/placebo or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, investigators should report any deaths, SAEs, or other AEs of concern that are considered related to prior treatment with the study drug. The investigator should follow each SAE and Grade ≥3 AE until the event has resolved to baseline grade, assessed as stable by the investigator, or until the patient withdraws consent or is lost to follow-up.

x. The first dosing day (Cycle 1 Day 1) should occur within 3 days from date of randomisation. All subsequent atezolizumab/placebo infusions may be administered with a window of ±3 days. The first dose of atezolizumab/placebo will be delivered over 60 (±15) minutes; if the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

y. **Gemcitabine** will be administered as a 30-minute IV infusion at a dose of 1000 mg/m^2 on Day 1 and Day 8 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations. **Carboplatin** will be administered after the completion of gemcitabine administration by short-term IV infusion over 15 to 60 minutes at AUC 2 on Day 1 and Day 8 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations. The first dosing day (Cycle 1 Day 1) should occur within 3 days from date of randomisation. All subsequent gemcitabine and carboplatin dosing on Day 1 may be administered within a window of ±3 days. Day 8 infusions of gemcitabine and carboplatin should not be administered any earlier than Day 7, but can be administered up to Day 11.

z. Patients should be instructed to take **capecitabine** 1000 mg/m^2 twice daily, approximately 12 hours apart orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle. In each cycle, the first dose of capecitabine should be taken in the evening of Day 1, and the last dose in the morning of Day 15. Patients should be instructed to return used and unused drug to the study site.

aa. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information until death, withdrawal of consent, loss to follow-up, or until study termination by the Sponsor. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits. Public information sources (e.g. county records) may also be used to obtain information about survival status only in case the patient withdrew from the study.

APPENDIX 2 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES

Global Study (Except Patients Enrolled in Mainland China):

Visit	Timepoint	Sample Type
Screening	Days -28 to -1	Mandatory FFPE tumour tissue sample [a]
During first line treatment		
Day 1, Cycle 1	Prior to first dose of any study treatment	Mandatory plasma sample for biomarker analysis
		Mandatory whole blood sample for germline DNA analysis [b]
Day 1 of Cycles 1 through 4	Prior to first dose of any study treatment	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)
Day 1, Cycles 1 and 3	30 ± 10 minutes after end of atezolizumab infusion	Atezolizumab PK (serum)
Day 1, Cycle 2	Prior to first dose of any study treatment	Optional FFPE tumour tissue sample [c]
		Mandatory plasma sample for biomarker analysis
Day 1, Cycle 3 and every 3 months thereafter	Prior to first dose of any study treatment	Mandatory plasma sample for biomarker analysis
Following discontinuation of study treatment		
At disease progression	NA	Optional FFPE tumour tissue sample [c]
		Mandatory plasma sample for biomarker analysis
Treatment Discontinuation Visit [d]	NA	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)

ADA = anti-drug antibody; NA = not applicable; PK = pharmacokinetics.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

a. Results of PD-L1 testing of this mandatory baseline tumour sample must be obtained from the designated central laboratory prior to enrolment. ER, PR, and HER2 triple-negative tumour status may be assessed locally prior to screening, and confirmed retrospectively by the designated central laboratory. If a fresh tumour sample is not available, the primary surgical resection sample or the most recent FFPE tumour biopsy sample may be used. The sample will be included in exploratory biomarker research. An FFPE block or at least 17 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

b. Mandatory whole blood for germline DNA isolation will be collected during the Baseline visit. If this sample has not been collected during the Baseline visit, it can be collected at any of the following cycles.

c. On-treatment tumour samples for biomarker analyses are optional. They must be collected within 14 days prior to treatment on Day 1 of Cycle 2 and at disease progression (±7 days) only if deemed clinically feasible by the investigator.

d. Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit 30 (±5) days after the last dose of study treatment.

China Population:

Visit	Timepoint	Sample Type
Screening	Days -28 to -1	Mandatory FFPE tumour tissue sample [a]
During first line treatment		
Day 1 of Cycles 1 through 4	Prior to first dose of any study treatment	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)
Day 1, Cycles 1 and 3	30 ± 10 minutes after end of atezolizumab infusion	Atezolizumab PK (serum)
Following discontinuation of study treatment		
Treatment Discontinuation Visit [b]	NA	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)

ADA = anti-drug antibody; NA = not applicable; PK = pharmacokinetics.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

a. Results of PD-L1 testing of this mandatory baseline tumour sample must be obtained from the designated central laboratory prior to enrolment. ER, PR, and HER2 triple-negative tumour status may be assessed locally prior to screening, and confirmed retrospectively by the designated central laboratory. If a fresh tumour sample is not clinically feasible, the primary surgical resection sample or the most recent formalin-fixed, paraffin-embedded (FFPE) tumour biopsy may be used. An FFPE block or at least 17 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. The sample will be included in exploratory biomarker research upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC), and upon the review and approval by the Human Genetics Resources Administration of China (HGRAC) exploratory application.

b. Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit 30 (±5) days after the last dose of study treatment.

   Note: Patients enrolled in mainland China will not undergo the following sample collections:

   - Optional FFPE tumour tissue collections on Day 1 of Cycle 2 and at disease progression.
   - Collection of whole blood sample for germline DNA analysis on Day 1 of Cycle 1
   - Collection of plasma samples for biomarker analysis on Day 1 of Cycles 1, 2, 3, and every 3 months thereafter.

APPENDIX 3 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: MODIFIED EXCERPT FROM ORIGINAL PUBLICATION

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

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

DEFINITION OF NON-MEASURABLE LESIONS

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

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm in diameter as assessed using calipers (e.g., skin nodules).

For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

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

CT AND MRI SCANS

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

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

Endoscopy, Laparoscopy, Ultrasound, Tumor Markers, Cytology, Histology

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NONTARGET LESIONS

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest

lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

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

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

- **Complete response (CR)**: disappearance of all target lesions

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

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

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

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

CRITERIA FOR NON-TARGET LESIONS

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

- **CR**: disappearance of all nontarget lesions and (if applicable) normalization of tumor marker level)

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

- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NONTARGET DISEASE

Patients with Measurable and Non-Measurable Disease

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

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply here as noted above. However, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging

modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

When patients have non-measurable (therefore nontarget) disease only, Table B is to be used.

Table A Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Nontarget Lesions)

Target Lesions	Nontarget 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

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

Table B Criteria for Overall Response at a Single Timepoint: Patients with Nontarget Lesions Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for nontarget disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

Special Notes on Response Assessment

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

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

Do not reproduce or distribute. The Sponsor will provide sites with official versions of all instruments to be completed in this study.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

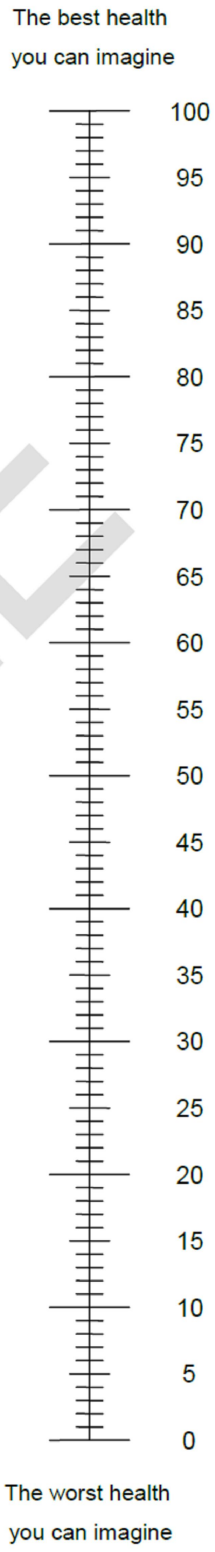
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



FACT-G (Single Item GP5)

GP5 (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4

Note:

Only item GP5 of the Physical Well-being domain of the FACT-4 instrument will be used in the current study.

APPENDIX 5 PREEXISTING AUTOIMMUNE DISEASES

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

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

APPENDIX 6 ANAPHYLAXIS PRECAUTIONS

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal use in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

APPENDIX 7 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

APPENDIX 8 COCKCROFT-GAULT FORMULA

Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula:

For females:

CrCl = 0.85 x ((140 - Age) / (Serum Creatinine)) x (Weight / 72)

For males:

CrCl = ((140 - Age) / (Serum Creatinine)) x (Weight / 72)

Where the units are:

- CrCl: mL/minute
- Age: years
- Weight: kg
- Serum creatinine: mg/dL

APPENDIX 9 GUIDE TO INTERPRETING THE AE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the study treatment.

- Time course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Sponsor would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge or rechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified.

APPENDIX 10 RISKS ASSOCIATED WITH ATEZOLIZUMAB AND GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH ATEZOLIZUMAB

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 immunomodulatory agents have been mild and 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 following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be* a *high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as* a *Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*
- The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered *in patients who are* deriving benefit and *have* fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's assessment of *the benefits and risks* and documented by the investigator. The Medical Monitor is available to advise as needed.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor 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. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 11.

Table 11 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 12.

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

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

Table 12 Management Guidelines for Hepatic Events

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

Event	Management

LFT = liver function tests.

[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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhoea or colitis are provided in Table 13.

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 bandemia): 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 13 Management Guidelines for Gastrointestinal Events (Diarrhoea or Colitis)

Event	Management
Diarrhoea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhoea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. *If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

Diarrhoea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Diarrhoea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist for evaluation and *confirmatory* biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 14.

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

Table 14 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid *drugs* such as methimazole or carbimazole as needed. • *Refer* to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Hyperglycaemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycaemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve, and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

Event	Management

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in table16 Table 15.

Table 15 Management Guidelines for Ocular Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 16.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnoea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. 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 preexisting 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 16.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 16. *Withhold treatment with atezolizumab for Grade 1 pericarditis*

and conduct a *detailed cardiac evaluation to determine the etiology and manage accordingly.*

Table 16 Management Guidelines for Immune-Mediated *Cardiac Events*

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, *Grades* 2–4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider *antiarrhythmic* drugs, temporary pacemaker, ECMO, VAD *or pericardiocentesis* as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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 (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, *antipyretic medications*, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs 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.

CRS 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 (Lee et al. 2019). CRS 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), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for *the* medical management of IRRs and CRS are provided in Table 17.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which

should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per per *investigator's* judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 17 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

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

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

Event	Management

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from *the* NCCN guidelines for *the* management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

[c] Symptomatic treatment may include oral or IV antihistamines, *antipyretic medications*, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

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 18.

Table 18 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.

Event	Management
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment*. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limiting, 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 19.

Table 19 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 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. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Stevens Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant), and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • Permanently discontinue atezolizumab for confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis.

[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 the equivalent of≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

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 20, *with specific guidelines for myelitis provided in* Table 21.

Table 20 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate aetiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate aetiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab* [b] – *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 21 *Management Guidelines for Immune-Mediated Myelitis*

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

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 being considered for 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 in Table 22.

Table 22 Management Guidelines for Immune-Mediated Meningoencephalitis

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

RENAL EVENTS

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. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate aetiology, should be treated according to the management guidelines for immune-mediated renal events in Table 23 below.

Table 23 Management Guidelines for Renal Events

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

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE Version 4.0.

[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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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 related event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among 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. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 24 below.

Table 24 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV 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 prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV 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 prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Event	Management

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone 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. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2019). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/L (100,000/μL)
  - ANC < 1.0×10^9/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis 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 (IL2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/μL)
  - AST ≥ 48 U/L

- Triglycerides > 1.761 mmol/L (156 mg/dL)
- Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines provided in Table 25.

Table 25 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • *If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).* • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

REFERENCES

La *Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.*

La *Rosée P, Horne A, Hines M,* et al. *Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.*

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

APPENDIX 11 VENTANA PD-L1 (SP142) ASSAY

VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody is intended for the qualitative immunohistochemical assessment of the programmed death ligand 1 (PD-L1) protein in formalin-fixed, paraffin-embedded (FFPE) breast carcinoma (BC) tissue stained with a BenchMark ULTRA instrument. It is indicated as an aid in identifying patients eligible for treatment with therapy targeting the interaction of PD-1 and PD-L1.

The clinical interpretation of any staining, or the absence of staining, must be complemented by histological studies and evaluation of proper controls. Evaluation must be made by a qualified pathologist within the context of the patient's clinical history and other diagnostic tests.

Patients are centrally screened for PD-L1 expression by the use of an investigational-use-only assay. Limited by Federal (or United States) law to investigational use.

DEVICE DESCRIPTION

VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody assay (VENTANA PD-L1 (SP142) assay) utilizes VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody (VENTANA PD-L1 (SP142) antibody) to recognize the PD-L1 protein. This assay is being developed as a companion diagnostic for identifying patients with breast carcinoma eligible for treatment with therapy targeting the interaction of PD-1 and PD-L1.

Details of the staining protocol and scoring criteria can be found in the investigational instructions for use included with the associated diagnostic study protocol.

VENTANA PD-L1 (SP142) assay utilizes a rabbit monoclonal primary antibody which binds to PD-L1 in paraffin-embedded tissue sections. The specific antibody can be localized using OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001) followed by OptiView Amplification Kit (Cat. No. 760-099 / 06396518001 (50 test) or 860-099 / 06718663001 (250 test)). Refer to the appropriate OptiView DAB IHC Detection Kit and OptiView Amplification Kit package inserts for further information (https://diagnostics.roche.com).

Signature Page for Protocol - MO39193 - TECENTRIQ - v9 - Global/Core - Published
System identifier: RIM-CLIN-465661

Approval Task	[redacted] Company Signatory 25-Jan-2023 20:54:29 GMT+0000