PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH PACLITAXEL COMPARED WITH PLACEBO WITH PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED INOPERABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	MO39196
VERSION NUMBER:	6.0
EUDRACT NUMBER:	2016-004024-29
IND NUMBER:	123277
NCT NUMBER:	NCT03125902
TEST PRODUCT:	Atezolizumab (MPDL3280A)
MEDICAL MONITOR:	[redacted], MD
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1.0: 14th February 2017
DATE AMENDED:	Version 2.0: 12th May 2017 Version 3.0: 5th December 2017 Version 4.0: 17th December 2018 Version 5.0: 23rd May 2019 Version 6.0: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Feb-2020 21:32:01	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
1	14 February 2017	—	—	—
2	12 May 2017	—	—	—
3	5 December 2017	China	4	29 May 2018
4	17 Dec 2018	China	5	07 Mar 2019
5	23 May 2019			
6	See date stamp above.			

PROTOCOL AMENDMENT, VERSION 6.0:
RATIONALE

Protocol MO39196 (IMpassion131) has been amended to update risks and management guidelines for atezolizumab to align with the latest Atezolizumab Investigator's Brochure. Changes to the protocol, along with a rationale for each change, are summarized below:

- To align with the Atezolizumab Investigator's Brochure, Version 15, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Sections 1.2.2.2, 5.1.2, 5.1.4, 5.1.5.2.1, 5.1.5.3.2, and Appendix 11).
- To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab (Section 5.1.2) and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome (Section 5.1.4.1 has been deleted and subsequent sections have been renumbered; new guidelines are in Appendix 11). In addition, systemic immune activation has been removed from the list of adverse events of special interest (Section 5.2.3).
- Serum pharmacokinetic/anti-drug antibody samples have been removed at Follow-Up in Appendix 1 as the assessment was already discontinued as of Protocol MO39196, Version 3.
- To address a request by the French ANSM, the atezolizumab adverse event management guidelines have been revised to add laboratory (e.g., B-type natriuretic peptide) and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis (Appendix 11).
- The management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for cytokine-release syndrome (CRS) to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Appendix 11).

The following table summarises the most important protocol revisions. It includes references to the amended sections of the protocol and a brief rationale for each update.

Type	High level summary of amendment	Protocol Section(s)
Safety Updates	• "Immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab. • Systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab, and management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome. • Management guidelines have been revised to add laboratory (e.g., B-type natriuretic peptide) and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis. • Management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for management of cytokine-release syndrome.	1.2.2.2, 5.1.2, 5.1.4, 5.1.4.1, 5.1.5.2.1, 5.1.5.3.2, 5.2.3, and Appendix 11
Schedule of Activities	• Serum pharmacokinetic/anti-drug antibody samples have been removed at Follow-Up as the assessment was already discontinued as of Protocol MO39196, Version 3.	Appendix 1

Additional minor changes have been made to improve clarity and consistency. This amendment represents changes from Version 5.0 of the protocol.

Amended Protocol Text

Changes in this document are marked as follows:

- Substantive new information appears in Book Antigua bold italics (***Book Antigua bold italics***) in the amended protocol.
- Deletions to text are **not** shown in the amended protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH PACLITAXEL COMPARED WITH PLACEBO WITH PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED INOPERABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
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MEDICAL MONITOR:	[redacted], MD
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 as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI−PD-L1 ANTIBODY) IN COMBINATION WITH PACLITAXEL COMPARED WITH PLACEBO WITH PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED INOPERABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
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VERSION NUMBER:	6.0
EUDRACT NUMBER:	2016-004024-29
IND NUMBER:	123277
NCT NUMBER:	NCT03125902
TEST PRODUCT:	Atezolizumab (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, safety, and pharmacokinetics (PK) of atezolizumab plus paclitaxel compared with placebo plus paclitaxel in patients with inoperable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for these conditions. 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 paclitaxel compared with placebo plus paclitaxel as measured by progression-free survival (PFS)	• PFS, defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause during the study, whichever occurs first. PFS will be tested hierarchically in the following fixed order:
	  • In the subpopulation with programmed death-ligand 1 (PD-L1)-positive tumour status.
	  • In the intent-to-treat (ITT) population.

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by overall survival (OS), 12-month and 18-month OS rates, health-related quality of life (HRQoL), 12-month PFS rate, objective response rate (ORR), duration of objective response (DoR), and clinical benefit rate (CBR)	• OS, defined as the time from randomisation to death from any cause in the PD-L1-positive subpopulation. • OS in the ITT population. • 12-month and 18-month OS rates. • Time to deterioration (TTD) in Global Health Status/HRQoL, defined by a minimally important decrease of ≥ 10 points on the Global Health Status /HRQoL scale (items 29 and 30) of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). • PFS rate at 12 months. • ORR, defined as the percentage of patients with measurable disease at baseline, who have achieved complete response (CR) or partial response (PR), as determined by the investigator using RECIST v1.1. • DoR, defined as the period from the date of initial CR or PR until the date of PD or death from any cause during the study, whichever occurs first. DoR is evaluated in the subset of patients with measurable disease at baseline, who have achieved an objective response. • CBR, defined as the percentage of patients who have achieved CR, PR, or stable disease (SD) that lasts at least 6 months. In addition, as per FDA request, 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).
Exploratory Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by second line PFS (PFS2)	• PFS2, defined as time from randomisation to tumour progression or death from any cause on next line of treatment, whichever occurs first.
• To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab plus paclitaxel compared with placebo plus paclitaxel, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23), using descriptive statistics	• Changes from baseline score in patient function (physical, role, social, emotional, cognitive) and disease/treatment-related symptoms by cycle, and between treatment arms as assessed by all function scales and symptom items/scales of the EORTC QLQ-C30 and QLQ-BR23.
• To evaluate PROs of Global Health Status/HRQoL scale associated with atezolizumab plus paclitaxel compared with placebo plus paclitaxel, as measured by the Global Health Status/HRQoL scale of the EORTC QLQ-C30, using descriptive statistics	• Changes from baseline score in HRQoL by cycle, and between treatment arms as assessed by the Global Health Status/HRQoL scale (items 29 and 30) of the EORTC QLQ-C30.

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives (cont.):	
• To evaluate and compare between treatment arms patient's health utility as measured by the European Quality of Life 5 Dimension (EQ-5D) questionnaire to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L (5-level version) questionnaire. • European Quality of Life Visual Analogue Scale (EQ-VAS).
• To evaluate the burden of treatment associated with the addition of atezolizumab to paclitaxel, as measured by the GP5 item 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 timepoint by treatment arm for item GP5 from the FACT-G
Specific Efficacy Objectives for patients recruited in China [1]:	
• The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by PFS 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.
Pharmacokinetic Objective:	
• To characterise the PK of atezolizumab when administered concomitantly with paclitaxel • To characterise the PK of paclitaxel when administered concomitantly with atezolizumab	• Serum concentration (C_{min} and C_{max}) of atezolizumab at specified timepoints • Plasma concentration (C_{min} and C_{max}) of paclitaxel at specified timepoints
Safety Objective:	
• To evaluate the safety of atezolizumab plus paclitaxel compared with placebo plus paclitaxel	• Incidence of adverse events (AEs), with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) • Change from baseline in targeted vital signs and physical findings • Change from baseline in targeted clinical laboratory test results

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. For patients who show evidence of immune-mediated toxicity, samples will be collected and tested for anti-nuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA), circulating anti-neutrophil cytoplasmic antibody (s-ANCA), and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA).
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objective:	
• To assess the activity and safety of atezolizumab according to PD-L1 status	• Relationship between PD-L1 protein expression by immunohistochemistry (Ventana® SP142 assay) in tumour tissues obtained within 3 months prior to patient randomisation [2], and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC 1/2/3).
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 tissues (obtained at baseline/within 3 months prior to randomisation [2], on-treatment, and at disease progression) and blood and their association with disease status and/or response to study drug. • To assess changes in blood- and tissue-based biomarkers during paclitaxel +/- 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 [CD]8) 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 by NGS genotyping in tumour tissues. • 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 paclitaxel +/- atezolizumab treatment. • Correlation of immune biomarker findings in blood and tissue samples from this study to findings from other studies in TNBC and other tumour types.

[1] Applicable only if the China-only recruitment is initiated.

[2] If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent sample should be used.

Study Design

Description of the Study

This is a Phase III, global, multicentre, randomised, double-blind, two-arm, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab (MPDL3280A, an anti-PD-L1 antibody) administered in combination with paclitaxel compared with placebo in combination with paclitaxel in patients with previously untreated, inoperable locally advanced or metastatic, centrally confirmed TNBC.

Patients will be enrolled in the study globally (Global study), which may be followed by additional enrolment in China only:

- **Global study:** Approximately 600 patients are planned to be randomised at approximately 200 sites globally (in select countries from Europe, Asia/Pacific, as well as North-, and South America). Patients will be randomised centrally, using an interactive voice or web response system (IxRS), in a 2:1 randomisation 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. Randomisation will be stratified by the following factors: tumour PD-L1 status (PD-L1 expression on tumour-infiltrating immune cells [ICs] assessed by immunohistochemistry [IHC]) (IC0 vs. IC1/2/3), prior taxane treatment (yes vs. no), presence of liver metastases (yes vs. no), and region (North America vs. Western Europe/Australia; vs. Eastern Europe/Asia Pacific vs. South America). Randomised patients will not be replaced.
- **Additional enrolment in China:** After approximately 600 patients have been randomised in the Global study, global recruitment will be closed. Additional patients may be subsequently randomised in China only, following the same randomisation procedures and ratio (2:1), to ensure a total enrolment of approximately 130 patients in mainland China (including patients 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. Analyses based on the China Population will be performed and summarised separately.

In the absence of disease progression or unacceptable toxicity, study treatment will continue until the end of the study (EOS; defined as last patient last visit, or LPLV). In the absence of disease progression, paclitaxel and atezolizumab/placebo may be discontinued for toxicity independently of each other, with the other treatment being continued. The Sponsor, patients, and investigators will not be aware of the patient's treatment assignment.

In order to evaluate the mechanism of action of the drug combination in the tumour microenvironment, its dependency on PD-L1 expression, changes in blood- and tissue-based biomarkers during treatment, as well as possible study treatment resistance mechanisms, paired tumour tissue biopsies will be collected close to the treatment start (mandatory sample), on-treatment (optional sample; collected pre-dose on Cycle 2, Day 1, prior to steroid medication), and at first evidence of radiographic disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (optional sample; collected if clinically feasible from a new or progressing tumour lesion).

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 until disease progression (PD), withdrawal of consent, death, or study

termination by the Sponsor, whichever occurs first. 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. Tumour assessments will be performed on the specified schedule regardless of treatment delays, interruptions or discontinuations. Radiologic imaging performed during the screening period should consist of 1) computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis, 2) bone scan or PET scan, 3) CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis, and 4) any other imaging studies (CT neck, plain films, etc.) as clinically indicated/determined by the treating physician. 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. For each patient, the same radiographic procedures and technique must be used for disease evaluation throughout the study (e.g., the same contrast protocol for CT scans and/or MRI). Evaluation of tumour response (e.g., for estimation of PFS, PFS rate, ORR, DoR and CBR) will be completed per RECIST v1.1. All primary imaging data used for tumour assessment will be collected by the Sponsor to enable centralised, independent review of response endpoints by an Independent Review Committee (IRC) (e.g., to meet potential requests by a reviewing Health Authority).

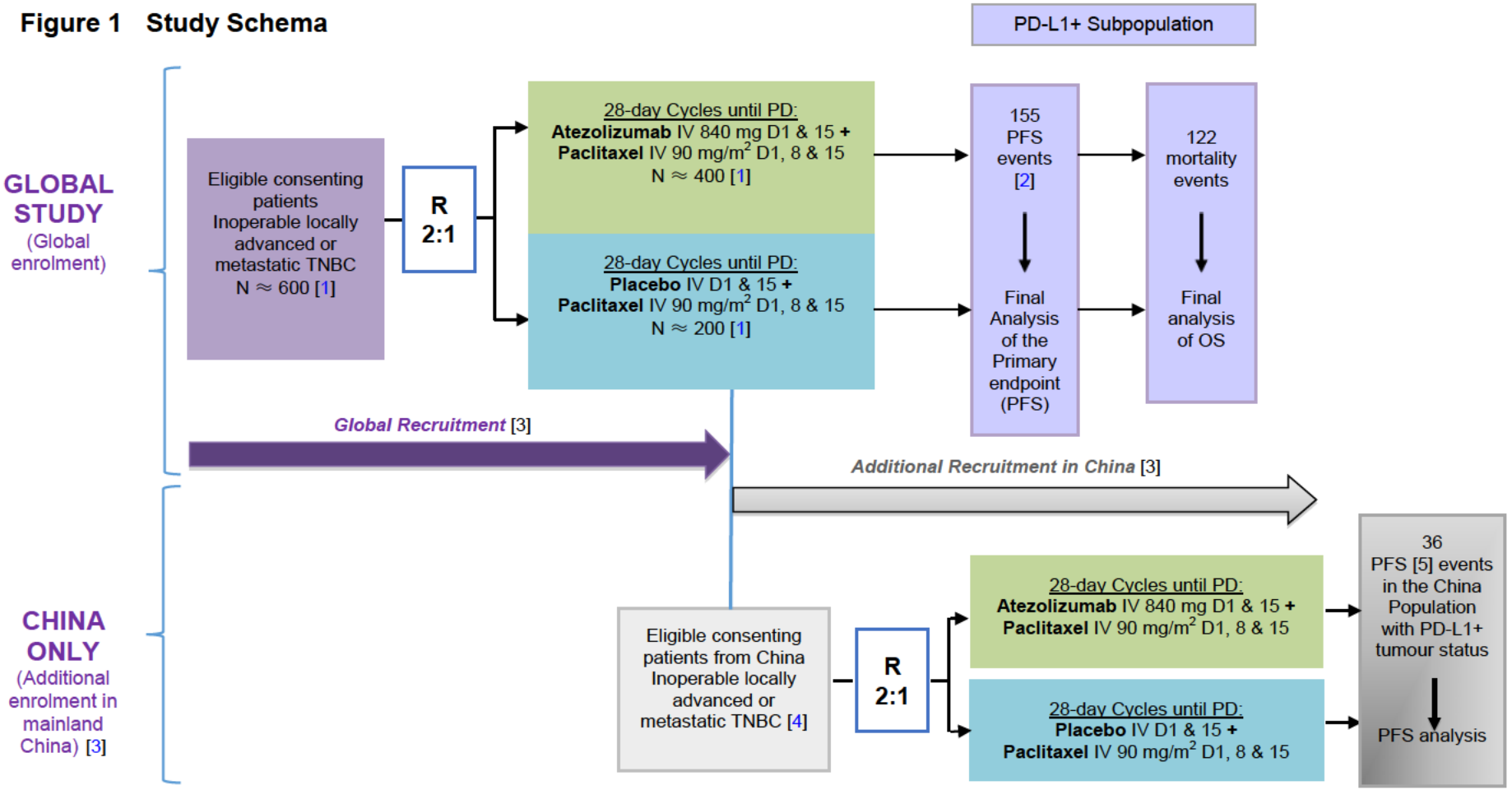
Patients randomised to either group must discontinue all study treatment upon determination of PD per RECIST v1.1. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled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

All patients who discontinued study treatment before EOS (including due to PD) will be followed for survival approximately every 3 months until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. Information regarding PFS2, PROs and the use of subsequent anti-cancer agents for metastatic TNBC will also be collected during the survival follow-up period. In addition, for patients who discontinue study treatment before EOS for reasons other than PD, tumour assessments will continue until PD, death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor.

The study Steering Committee (SC) will provide scientific oversight for the trial. Details on 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. Details on the composition of the iDMC and safety review plan 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; IV= intravenous; PD= disease progression; R = randomisation; RECIST=Response Evaluation Criteria In Solid Tumors; TNBC=triple-negative breast cancer

[1] Based on the results of the IMpassion130 study, it is estimated that approximately 40% of the enrolled patients will have PD-L1-positive tumour status.

[2] The final (and considered primary) analysis of PFS will occur when approximately 155 PFS events have occurred in the PD-L1+ subpopulation. OS will also be analysed at the final analysis of PFS.

[3] Additional recruitment in mainland China may only commence after global recruitment is completed.

[4] Additional recruitment in mainland China will continue until the total number of patients from China (including those enrolled in the Global study) reaches ≈ 130

[5] Based on the China Population (n≈130; including patients from China enrolled in the Global study)

Number of Patients

Approximately 600 patients will be randomised at approximately 200 sites globally (Global study). This total accounts for an estimated 10% drop-out rate during the study. Based on the results of the IMpassion130 study (Schmid et al. 2018), it is estimated that approximately 40% of the enrolled patients will have PD-L1-positive tumour status.

As described above, after approximately 600 patients have been randomised, global recruitment will be closed. Additional patients may be subsequently randomised in mainland China only, following the same randomisation procedures and ratio (2:1), to for enrolment of approximately 130 patients in mainland China (including patients from China enrolled in the Global study).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Women or men aged ≥18 years
3. Patients with locally advanced or metastatic, histologically documented TNBC (absence of human epidermal growth factor 2 [HER2], oestrogen receptor [ER], and progesterone receptor [PR] expression), not amenable to surgical therapy.
    a. HER2 negativity is defined as either of the following: IHC 0, IHC 1+ or IHC2+/*in situ* hybridisation (ISH)- as per American Society of Clinical Oncology (ASCO)-College of American Pathologists Guideline (CAP) guideline (ISH- is defined as a ratio of HER2 to CEP17 <2.0) (Wolff et al. 2018).
    b. ER and PR negativity are defined as <1% of cells expressing hormonal receptors via IHC analysis as per ASCO-CAP guideline (Hammond et al. 2010).
4. Eligible for taxane monotherapy.
5. No prior chemotherapy or targeted systemic therapy (including endocrine therapy) for inoperable locally advanced or metastatic TNBC.

Prior radiation therapy for metastatic 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.

Previous chemotherapy for early breast cancer (eBC; neoadjuvant or adjuvant setting) is permitted if completed ≥12 months before randomisation.

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.

6. Availability of formalin-fixed paraffin-embedded (FFPE) tumour block (preferred) or at least 17 unstained slides, collected ≤3 months prior to randomisation, with an associated pathology report, if available. If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent 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 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 for PD-L1 testing, and the score measured in the most recent sample prior to enrolment will be used as the PD-L1 score for patient stratification.

   i. Acceptable samples include core needle biopsies for deep tumour tissue (more than one core if clinically feasible) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

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

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

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

8. Life expectancy ≥ 12 weeks

9. Measurable disease, as defined by RECIST v1.1. (Note: Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.)

10. Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment (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 Cycle 1, Day 1)

b. Lymphocyte count ≥ 500/μL

c. Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

d. Haemoglobin ≥ 9.0 g/dL

   Patients may be transfused or receive erythropoietic treatment to meet this criterion.

e. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5× the upper limit of normal (ULN), with the following exceptions:

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

   ii. Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5× ULN

f. Serum bilirubin ≤ 1.25× ULN

   Patients with known Gilbert's disease who have serum bilirubin level ≤ 3× ULN may be enrolled.

g. International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5× ULN

   This applies only to patients who are not receiving an anticoagulant medicinal product; patients receiving an anticoagulant medicinal product should be on a stable dose and have an INR which is not above the target therapeutic range.

h. Calculated creatinine clearance (CrCl) ≥30 mL/min (Cockcroft-Gault).

11. Negative human immunodeficiency virus (HIV) test at screening.

12. Negative hepatitis B surface antigen (HBsAg) test at screening.

13. 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 positive HBcAb test.

14. 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 a positive HCV antibody test.

15. Women of child bearing potential must agree to either use a contraceptive method with a failure rate of ≤1% per year or to remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 5 months after the last dose of atezolizumab/placebo, or for at least 6 months after the last dose of paclitaxel.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilisation (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of ≤1% per year include bilateral tubal ligation, male sterilisation, 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 acceptable methods of contraception.

16. Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

17. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

a. 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 6 months after the last dose of paclitaxel. Men must refrain from donating sperm during this same period.
b. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study 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.

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 at least 2 weeks prior to randomisation

2. Known central nervous system (CNS) disease, except for treated asymptomatic CNS metastases, provided all of the following criteria are met:

   a. Measurable disease outside the CNS

   b. Metastases are limited solely to cerebellar and supratentorial lesions (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

   c. No ongoing requirement for corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed)

   d. No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomisation

   e. No evidence of progression or haemorrhage after completion of CNS directed therapy

      Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible if all other criteria above are met.

3. Leptomeningeal disease

4. Uncontrolled pleural effusion, pericardial effusion, or ascites (Note: patients with indwelling catheters, such as PleurX® are allowed)

5. Uncontrolled tumour-related pain

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

   b. 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. There is no required minimum recovery period.

   c. 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.

6. Uncontrolled hypercalcemia (>1.5 mmol/L [>6 mg/dL] ionized calcium or serum calcium [uncorrected for albumin] >3 mmol/L [>12 mg/dL] or corrected serum calcium > ULN) or clinically significant (symptomatic) hypercalcemia.

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

7. Malignancies other than TNBC within 5 years prior to randomisation, with the

exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer).

General Medical Exclusion Criteria

8. Pregnant or lactating women, or intending to become pregnant during the study.

9. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome).

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

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

    b. 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.

11. Presence of an abnormal electrocardiogram (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.

12. Serious infection requiring antibiotics within 2 weeks prior to randomisation, including but not limited to infections requiring hospitalisation or IV antibiotics, such as bacteraemia, or severe pneumonia.

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. Note: 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 30 days prior to initiation of study treatment.

15. Inability to understand the local language(s) for which the Patient Reported Outcome (PRO) questionnaires are available.

Exclusion Criteria Related to Atezolizumab

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

17. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells or any component of the atezolizumab formulation.

18. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis (MS), vasculitis, or glomerulonephritis.

(Note: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.)

19. Prior allogeneic stem cell or solid organ transplantation

20. History of idiopathic pulmonary fibrosis (IPF, including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan. (Note: History of radiation pneumonitis in the radiation field [fibrosis] is permitted.)

21. Current treatment with anti-viral therapy for HBV.

22. Active tuberculosis.

23. Receipt of a live, attenuated vaccine within 4 weeks prior to randomisation or anticipation that such a live, attenuated vaccine will be required during the study.

Note: Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to randomisation, during treatment or within 5 months following the last dose of atezolizumab/placebo.

24. Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or immune checkpoint 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 immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to randomisation, or anticipated requirement for systemic immunosuppressive medications during the trial.

a. Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.

b. Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumour assessments performed using MRI.

c. The use of corticosteroids (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

d. Systemic corticosteroids are allowed as paclitaxel premedication during the trial at a dose ≤10 mg dexamethasone or equivalent in order to avoid severe hypersensitivity reactions.

27. Poor peripheral venous access

28. Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment

29. Any other serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study.

Exclusion Criteria Related to Paclitaxel

30. History of hypersensitivity reactions to paclitaxel or other drugs formulated in the same solvent as paclitaxel (polyoxyethylated castor oil).

End of Study

The EOS is defined as the date when the last patient, last visit (LPLV) is completed.

Global Study

This is an event driven trial. The Global study will end after the required number of events for the final analysis of OS has been reached.

In addition, the Sponsor may decide to terminate the study at any time.

China Population

For patients randomised during additional enrolment in China, the study will end when the pre-specified number of 36 PFS events has occurred in the China population with PD-L1-positive tumour status, or when the Global study ends, whichever is later.

In case additional enrolment in China is not initiated, patients from China enrolled in the Global study will end the study as defined for all other patients in the Global study.

Length of Study

The length of the study and the time for final analysis will depend on the actual enrolment 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.

Investigational Medicinal Products

Atezolizumab/placebo and paclitaxel are considered investigational medicinal products (IMPs) in this study. All IMPs will be supplied by the Sponsor.

Atezolizumab (Investigational Drug)

The atezolizumab drug product is provided in a single-use, 20cc USP/Ph. Eur. Type 1 glass vials intended for IV administration. The vial contains ~20 mL (1200 mg) of atezolizumab solution (60 mg/mL).

Placebo (Comparator)

Placebo will consist of the vehicle without the antibody. Placebo will be supplied in a single-use, 20cc glass vials containing ~20 mL of solution.

Patients will receive atezolizumab 840 mg (corresponding to 14 mL from drug product, in 250 mL 0.9% sodium chloride [NaCl]) or matching placebo by IV infusion administered on Day 1 and Day 15 (± 3 days) of every 28-day cycle. 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. 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.

Administration of atezolizumab/placebo will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Atezolizumab (or placebo) infusions will be administered per the instructions outlined in the current atezolizumab Investigator's Brochure (IB).

Paclitaxel (Background Chemotherapy)

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

Paclitaxel will be administered at the 90 mg/m^2 dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. In the absence of unacceptable toxicity, paclitaxel will be administered until PD or until the end of the study, whichever occurs earlier.

All patients should be premedicated prior to paclitaxel administration to prevent severe hypersensitivity reactions. Prior to receiving the first two study infusions of paclitaxel, all patients will receive corticosteroids (8-10 mg dexamethasone or equivalent) as part of either the institutional standard of care or the following premedication:

- Dexamethasone 8-10 mg (or equivalent) administered orally approximately 12 and 6 hours prior to the paclitaxel infusion

  Patients may be treated with dexamethasone ≤10 mg IV within 1 hour prior to the paclitaxel infusion if the patient did not take the oral dexamethasone.
- Diphenhydramine 50 mg IV (or equivalent) 30-60 minutes prior to the paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30-60 minutes prior to paclitaxel infusion.

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 to the extent that is clinically feasible. For example, if paclitaxel is well tolerated during the first two weekly infusions without apparent hypersensitivity reaction, a reduction in the dose of dexamethasone premedication (or equivalent) should be considered for subsequent cycles if permitted by institutional standard of care. This approach has been reported to be successful in the literature (Berger et al. 2012).

Details on paclitaxel dose modifications due to toxicity are provided in Section 5.1.5.3.2.

Sites should follow their institutional standard of care for determining the paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

Atezolizumab/placebo and paclitaxel may be discontinued for toxicity independently of each other in the absence of PD.

Non-Investigational Medicinal Products

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

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel in patients with inoperable locally advanced or metastatic TNBC based on the following primary efficacy endpoint:

- Progression-free survival (PFS), defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause during the study, whichever occurs first.

PFS will be tested hierarchically in the following fixed order:

- PFS in the PD-L1-positive subpopulation (defined as patients in the intent-to-treat [ITT] population whose PD-L1 status is IC1/2/3 at the time of randomisation).
- PFS in the ITT population (defined as all randomised patients, whether or not the assigned study treatment was received).

PFS will be compared between treatment arms based on the stratified log-rank test. The stratification factors will be three of the four predefined randomisation stratification factors: tumour PD-L1 status (IC0 vs. IC1/2/3), prior taxane treatment (yes vs. no) and presence of liver metastases (yes vs. no) and will be obtained from the interactive Web/phone response system (IxRS). The hazard ratio (HR) for disease progression or death will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

Data for patients without disease progression or death will be censored at the last tumour assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumour assessment prior to the missed visits as a sensitivity analysis. If no tumour assessment was performed after randomisation, data will be censored at the date of randomisation + 1 day.

The final analysis of the primary endpoint (PFS) in the China population will be conducted after approximately 36 PFS events have been documented in the China population with PD-L1-positive tumour status. Methods for analysing data from the China population will be provided in the Statistical Analysis Plan (SAP). 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.

Determination of Sample Size

Global Study

The purpose of this event-driven study is to evaluate the efficacy of atezolizumab plus paclitaxel compared to placebo plus paclitaxel as measured by PFS (either investigator-assessed disease progression per RECIST v1.1 or death from any cause, whichever occurs first). PFS will be assessed hierarchically in the following fixed order: (1) PFS in the PD-L1-positive subpopulation; followed by (2) PFS in the ITT population.

The sample size for the Global study is determined based on the following assumptions:

- Median PFS of 5.0 months in patients with PD-L1-positive tumour status randomised to the placebo plus paclitaxel group (as detected in patients with PD-L1-positive TNBC in the placebo plus albumin-bound (nab-)paclitaxel control arm of the IMpassion130 study) (Schmid et al. 2018);
- Treatment effect (between-group difference) of 2.5 months in the median PFS (HR 0.62) in the PD-L1-positive subpopulation (as detected in the PD-L1-positive subpopulation of the IMpassion130 study) (Schmid et al. 2018);
- Randomisation ratio of 2:1;
- Approximately 40% of the enrolled patients are expected to have PD-L1-positive tumour status (as detected in the IMpassion130 study) (Schmid et al. 2018);
- 80% power and an overall 2-sided α of 0.05;
- Drop-out rate of 10%.

Based on these assumptions and parameters, approximately 213 evaluable patients with PD-L1-positive tumour status (approximately 142 in the atezolizumab plus paclitaxel group and approximately 71 in the placebo plus paclitaxel group) and a total of 155 PFS events are required to detect a between-group difference of 2.5 months in the final analysis of median PFS (HR 0.62). Assuming that approximately 40% of the enrolled patients will have PD-L1-positive tumour status, and to account for an estimated drop-out rate of 10%, approximately 600 patients will be randomised in the Global study (approximately 400 in the atezolizumab plus paclitaxel group and approximately 200 in the placebo plus paclitaxel group). Anticipating a global recruitment period of approximately 23 months (up to 40 patients per month), the clinical cut-off (CCO) date for the primary (final) PFS analysis in the subpopulation with PD-L1-positive tumour status is expected to occur approximately 29 months after the first patient was randomised (FPI) in the Global study.

In addition, overall survival (OS) is a secondary analysis in this study. As for the primary analysis of PFS, OS will be analysed in the PD-L1-positive subpopulation and ITT population. Based on the previously noted assumptions, with an anticipated global recruitment period of approximately 23 months (up to 40 patients per month) and assuming that in the subpopulation with PD-L1-positive tumour status, median OS will be 15.5 months in the placebo plus paclitaxel group (based on the median OS in the PD-L1-positive subpopulation receiving nab-paclitaxel only in the IMpassion130 study (Schmid et al. 2018), the study will have approximately 70% power to detect a between-group difference of 9.5 months in the median OS (HR 0.62). The final analysis of OS should occur after 122 mortality events have been observed in the subpopulation with PD-L1-positive tumour status, which is expected approximately 40 months after FPI. By this time-point, 305 mortality events are expected to have occurred in the ITT population.

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: [1] PFS by RECIST v1.1 in the PD-L1-positive subpopulation; [2] PFS by RECIST v1.1 in the ITT population;
- Secondary: [3] overall survival (OS) in the PD-L1-positive subpopulation; [4] OS in the ITT population; [5] ORR by RECIST v1.1 in the PD-L1-positive, Response-evaluable subpopulation; [6] ORR by RECIST v1.1 in the ITT population.

Further details will be included in the SAP.

China Population

After approximately 600 patients have been randomised in the Global study, global recruitment will be closed. Additional patients may be subsequently enrolled in China only, following the same randomisation procedures and ratio (2:1), for a total of approximately 130 patients from mainland China (including patients enrolled in the Global study), referred to as the China Population.

The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel 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).

Further details will be included in the SAP.

Interim Analyses

No interim analysis of PFS is planned.

An interim analysis of OS will be performed (in the PD-L1-positive subpopulation and the ITT population) at the primary (final) analysis of PFS. A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets, 1983). Testing on OS will be conducted hierarchically only if the null hypothesis for testing on PFS has been rejected.

The iDMC will complete periodic reviews of safety data.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody (also known as anti-therapeutic antibody, ATA)
AE	adverse event
ALT	alanine transaminase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ATA	anti-therapeutic antibody
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
c-ANCA	circulating anti-neutrophil cytoplasmic antibody
CAP	College of American Pathologists
CBR	clinical benefit rate
CCO	clinical cut-off (date)
CD	cluster of differentiation
C-DoR	duration of response for confirmed responders
CEP17	centromeric probe for chromosome 17
CNS	central nervous system
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
C-ORR	confirmed objective response rate
CrCL	creatinine clearance
CRO	Contract Research Organisation
CSR	clinical study report
CT	computed tomography
DEHP	di-(2-ethylhexyl)phthalate
DNA	deoxyribonucleic acid
DoR	duration of objective response
DRB	Data Review Board
eBC	early breast cancer
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOS	end of study
ePRO	electronic patient-reported outcome
ER	(o)estrogen receptor
ESMO	European Society for Medical Oncology
EQ-5D-5L	European Quality of Life 5 Dimension, 5-level version
FFPE	formalin-fixed paraffin-embedded
FPI	first patient in
G-CSF	granulocyte colony stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigators Brochure
IC	immune cell
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IHC	Immunohistochemistry
Ig	Immunoglobulin
IL	Interleukin
IMP	investigational medicinal product
IND	Investigational New Drug application
INR	International Normalized Ratio
IRC	Independent Review Committee
IRR	infusion-related reaction
ISH	*in situ* hybridization
ITT	intent to treat
IV	Intravenous
IxRS	interactive voice/web response system
LPI	last patient in
LPLV	last patient last visit

Abbreviation	Definition
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MRI	magnetic resonance imaging
TNBC	triple-negative breast cancer
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	Progression of disease / disease progression
PD−1	programmed death−1
PD−L1	programmed death−ligand 1
PFS	progression-free survival
PK	Pharmacokinetic
PR	progesterone receptor/partial response
PRO	patient-reported outcome
PVC	Polyvinylchloride
QLQ-BR23	breast cancer module for QLQ-C30
QLQ-C30	Quality of Life Questionnaire Core 30
RA	rheumatoid arthritis
RBC	red blood cell
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAP	Statistical Analysis Plan
SD	stable disease
SLE	systemic lupus erythematosus
TNBC	triple-negative breast cancer
TNF	tumour necrosis factor
ULN	upper limit of normal
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Breast cancer 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 of America (USA), it is projected that there will be 246,660 new diagnoses (not including about 61,000 cases of female breast carcinoma *in situ*) due to BC, and an estimated 3,560,570 women will be living with BC in 2016 (Siegel et al. 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 localized 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 USA, it is projected that there will be 40,450 deaths due to BC in 2016 (Siegel et al. 2016; Miller et al. 2016). 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 oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (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). Most new treatment options for mBC are only effective for ER/PR-positive or HER2-positive metastatic tumours (Zeichner et al. 2016). The 5-year survival rate following metastatic diagnosis is around 15% (Jemal et al. 2011; Ferlay et al. 2013).

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), 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 hybridisation (ISH) negative using single-probe ISH or dual-probe ISH (Wolff et al. 2018).

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 et al. 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. In general, anthracycline-based combination therapy and taxanes such as paclitaxel and docetaxel are believed to show the greatest activity (Piccart-Gebhart et al. 2008). Given the use of regimens containing anthracyclines in the adjuvant setting and the risk of cardiotoxicity associated with repeated courses, taxanes are now the most commonly used agent for patients with locally advanced or metastatic disease, particularly in the front-line setting (Greene and Hennessy, 2015).

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 Taxanes and Paclitaxel in Metastatic Breast Cancer

Taxane-based regimens are considered a standard of care option in first-line therapy for patients with mBC, including TNBC (Cardoso et al. 2012). No standard approach exists for second- or further-line treatment, and options for cytotoxic chemotherapy are the same as those for other subtypes. Single-agent cytotoxic chemotherapeutic agents are generally regarded as the primary option for patients with metastatic TNBC, although combination chemotherapy may be used when there is aggressive disease and visceral involvement.

The role of paclitaxel in the treatment of BC is well established. The response rates for paclitaxel administered as a single agent to patients with mBC are approximately 25% in first-line treatment (Wilson et al. 1994; Seidman et al. 1995; Nabholtz et al. 1996; Gradishar et al. 2005).

Weekly paclitaxel (80–90mg/m^2) is currently considered the most effective schedule for delivering paclitaxel (Swanton 2011), and was found to be associated with higher overall survival (OS) and lower incidence of serious adverse events, neutropoenia, neutropoenic fever, and peripheral neuropathy compared with the three-weekly taxane schedules in advanced breast cancer (Seidman et al. 2008; Mauri et al. 2010). In addition, a regimen consisting of weekly paclitaxel administrations for three weeks, followed by one-week break was reported to be associated with less neurotoxicity compared to continuous weekly administrations (Swanton 2011); refer to Section 3.3.3 for further details.

1.1.2.2 PD-L1 Inhibitors in the Treatment of TNBC

Recent 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 (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 (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 results of early clinical studies, blockade of the PD-1/PD-L1 axis with atezolizumab (Emens et al. 2018; Adams et al. 2018; Schmid et al. 2018), pembrolizumab (Nanda et al. 2016; Adams et al. 2019a; Adams et al. 2019b), or avelumab (Dirix et al. 2018) has demonstrated promising efficacy and durable responses in patients with advanced TNBC.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (TECENTRIQ™, formerly known as MPDL3280A) is a humanised immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary (CHO) cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumours and haematologic malignancies in humans. Atezolizumab has been approved in the USA for the treatment of locally advanced or metastatic urothelial carcinoma, metastatic non-small cell lung cancer (NSCLC), and PD-L1-positive unresectable locally advanced or metastatic TNBC.

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 intravenous (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 most recent version of the atezolizumab Investigator's Brochure for study descriptions).

Anti-tumour activity, as determined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 responses, has been observed across multiple advanced tumour types for both atezolizumab monotherapy (Phase 1a study PCD4989g) as well as in combination with bevacizumab and/or chemotherapy (Phase 1b study GP28328). In patients with mTNBC, atezolizumab has shown activity as monotherapy (Emens et al. 2018; Schmid et al. 2017), and in combination with nab-paclitaxel (Adams et al. 2018; Schmid et al. 2018). 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). Among 115 objective response rate (ORR)-evaluable patients, investigator-assessed confirmed ORR was 10% (95% CI, 5-16) with 3 complete responses (CRs) and 8 partial responses (PRs). Median duration of objective response (DoR) was 21 months (range 9.6 weeks to non-estimable [NE]) and all-patient median OS was 8.9 months (95% CI, 7.0-12.6), with a median follow-up duration of 25.3 months. Median progression-free survival (PFS) was 1.4 months (95% CI, 1.4–1.6). 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, 7.1–14.7] vs 7.0 [95% CI, 5.1–12.6], 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–NE], vs. 7.3 months [95% CI, 6.1–10.8], respectively). Median PFS was consistent (approximately 1.4 months) regardless of PD-

L1 expression or line of therapy (Atezolizumab Investigator's Brochure, 2018). 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

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 (Roche Data on File).

Adverse Events in the mTNBC Subpopulation of Study PCD4989g

Of the 116 safety-evaluable TNBC patients, 114 (98.3%) reported one or more adverse events (AEs). A total of 59 (50.9%) patients experienced Grade 3 - 4 AEs based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Treatment-related Grade 3-4 events occurred in 13 (11.2%) of patients. Serious adverse events (SAEs) were reported for 51 patients (44.0%). Grade 5 AEs (not including deaths due to cancer progression) occurred in three patients (2.6%). Adverse events led to atezolizumab discontinuation in five (4.3%) patients (Roche Data on File).

Long-term follow-up data from 115 safety-evaluable patients in study PCD4989g (data cut-off Mar 31, 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 AE. The most common AEs (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 AEs 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 AEs (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 AEs, 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 (SAEs) 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 AEs (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 (Roche Data on File).

Immune-Mediated Adverse Events

The safety data presented in this section is based on pooled data from 3075 patients with multiple tumour types and supporting data from the estimated cumulative exposure in >16,000 patients across all clinical trials.

Given the mechanism of action of atezolizumab, events associated with inflammation and/or *immune-mediated* AEs have been closely monitored during the atezolizumab clinical program. Important identified risks associated with atezolizumab include the occurrence of the following immune-mediated AEs (listed with total frequencies of these events in pooled clinical trials of atezolizumab): *immune-mediated* pneumonitis (2.8% [86/3075]); *immune-mediated* hepatitis (2.0% [62/3075]); *immune-mediated* colitis (1.1% [34/3075]); *immune-mediated* pancreatitis (0.5% [16/3075]); *immune-mediated* endocrinopathies, including diabetes mellitus (0.3% [10/3075]), hypothyroidism (4.8% [149/3075]), hyperthyroidism (0.9% [28/3075]), and adrenal insufficiency (0.4% [12/3075]); *immune-mediated* myositis occurred in <0.2% (4/3075); *immune-mediated* hypophysitis (<0.1% [1/3075]); *immune-mediated* neuropathies, including myasthenic syndrome/myasthenia gravis (<0.1% [4/3075]), and Guillain-Barré syndrome (0.2% [5/3075]); *immune-mediated* meningoencephalitis (0.4% [12/3075]); *immune-mediated* myocarditis (<0.1% [2/3075]), and *immune-mediated* nephritis (<0.1% [1/3075], representing one case of Henoch-Schoenlein purpura nephritis) (Atezolizumab Investigator's Brochure, 2018). Overall, the nature and frequency of *immune-mediated* AEs has been consistent across multiple tumour types in clinical studies of atezolizumab.

Excessive activation of the immune system is a potential risk associated with atezolizumab and has been observed when used in combination with other immune-modulating agents.

Treatment-emergent (treatment-induced plus treatment-enhanced) anti-drug antibodies (ADAs) were detected at one or more post dose time-points in 31.7% (139/439) patients in Study PCD4989g. The presence of ADAs did not appear to have a clinically significant impact on PK, safety, or efficacy.

Refer to the atezolizumab Investigator's Brochure for additional details 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 1b 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) 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. 2018). 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, 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 is currently being 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) showed that after a median follow-up of 12.9 months, 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 0.69-0.92, p=0.0025). In the PD-L1-positive population, median PFS was 7.5 vs. 5.0 months in the two groups, respectively; HR=0.62, 95% CI: 0.49-0.78, 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: 0.69-1.02, 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: 0.45-0.86). 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% vs 43% in the two groups, respectively (treatment difference 16%, p=0.0016). Median DoR was 7.4 months vs 5.6 months in the two groups, respectively in the ITT population, and 8.5 months vs 5.5 months, respectively in the PD-L1-positive subpopulation (Schmid et al. 2018). 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 metastatic TNBC patients whose tumours are PD-L1-positive.

1.2.2.4 Safety of Atezolizumab Combined with Chemotherapy

Adverse Events in the mTNBC Subpopulation of Study GP28328

As of 30 April 2017, all 33 (100%) safety-evaluable mTNBC patients experienced at least one AE. Consistent with the known toxicity profiles of atezolizumab and nab-paclitaxel, the most commonly occurring AEs (≥30%) were fatigue (66.7%), diarrhoea (51.5%), alopecia (42.4%), nausea, constipation, and cough (39.4% each), pyrexia, and neutrophil count decreased (36.4% each), neutropoenia (33.3%), and peripheral neuropathy (30.3%). All 33 (100%) safety-evaluable mTNBC patients experienced at least one treatment-related AE.

Over three-quarters of the patients with TNBC (84.4%) had a Grade 3-4 event. Of these, neutrophil count decreased (27.3%), neutropoenia (18.2%), anaemia and AST increased (9.1% each), and thrombocytopoenia, diarrhoea, pneumonia, sepsis, platelet count decreased, white blood cell count decreased, hyponatraemia, and arthralgia (6.1% each) occurred in more than 1 patient (>3%). Twenty-four patients (72.7%) experienced a related Grade 3-4 event; of these, only neutrophil count decreased (9.1%) and pneumonia and thrombocytopenia (6.1%) were reported for more than one patient (>3%).

Seventeen (51.5%) TNBC patients experienced a SAE; of these, the event was assessed as related to study treatment in seven patients (1821.2%): pneumonia, (6.1%), diarrhoea, pyrexia, anaemia, and pneumonia mycoplasmal (3.0% each). None of the patients with TNBC experienced a Grade 5 AE, and two patients (6.1%) with TNBC discontinued atezolizumab due to an AE.

Adverse Events in the Overall Population of Study GP28328

As of the data cut-off of 30 April 2017, there were 229 safety-evaluable patients enrolled across six treatment arms in Study GP28328. All 229 (100%) safety-evaluable patients reported at least one AE, 171 patients (74.7%) experienced a Grade 3-4 AE, 112 (48.9%) experienced an SAE, and 22 (9.6%) experienced an AE leading to discontinuation of atezolizumab. Grade 5 AEs occurred in two of the 76 patients in the NSCLC cohorts.

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 AEs associated with either agent individually. The AEs 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 data cut-off of 17 April 2018, AEs occurred in 99.3% vs 97.9% in the atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel groups, respectively, and Grade 3-4 AEs occurred 48.7% vs 42.2% 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 and hypothyroidism. The only Grade 3-4 AEs occurring in >5% of patients were neutropenia reported in 8.2% of patients in each group), and peripheral neuropathy (reported in 5.5% of patients in the atezolizumab plus nab-paclitaxel group compared to 2.7% of patients in the placebo plus nab-paclitaxel group).

Three of the six fatal AEs in the atezolizumab plus nab-paclitaxel group (autoimmune hepatitis [considered related to blinded atezolizumab], septic shock [considered related to nab-paclitaxel], mucosal inflammation [considered related to nab-paclitaxel]) and one of three fatal AEs in placebo plus nab-paclitaxel group (hepatic failure [considered related to blinded atezolizumab and nab-paclitaxel]) were assessed as treatment-related. One patient in each group experienced a Grade 5 AESIs (autoimmune hepatitis in the atezolizumab plus nab-paclitaxel group and hepatic failure in the placebo plus nab-paclitaxel group). Grade 3-4 AESIs occurred in 7.5% and 4.3% 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 Clinical Study Report; Roche Data on File).

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 in the dose range of 1 mg/kg to 20 mg/kg, the typical population clearance (CL) 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. 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, gender, positive ATA status, albumin levels, tumour burden, region or ethnicity, 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.

The development of ADAs has been observed in patients at all dose levels. ADA positivity had no major effect on atezolizumab concentrations and PK although there was a trend for lower C_{min} values in the ADA positive subgroup in Study PCD4989g. The presence of ADAs did not appear to have a clinically significant impact on PK, safety, or efficacy of atezolizumab. A Phase I population PK analysis that included 472 patients from Studies PCD4989g and JO28944 found that positive ADA status against atezolizumab led to approximately 13% reduction in overall exposure (Atezolizumab Investigator's Brochure, 2018).

In all safety-evaluable patients with available post-treatment ADA status in the atezolizumab safety database (n = 2007), the incidence of hypersensitivity events and infusion-related reactions was low and numerically higher in ADA-positive than ADA -negative patients. Hypersensitivity events were reported in 24 patients (1.2%): 9 ADA-negative (0.7%) and 15 ADA-positive (1.9%) patients. Infusion-related reactions occurred in 25 patients (1.2%): 14 ADA-negative (1.1%) and 11 ADA-positive (1.4%) patients. The incidences of all grade adverse events, Grade 5 AEs, AEs leading to treatment discontinuation, AEs leading to dose interruption, and AESIs were similar irrespective of post-baseline ADA status (negative or positive). Numerical differences were observed in Grade 3–4 AEs (40.7% in ADA-negative vs. 47.0% in ADA-positive patients), but no individual preferred terms could be identified to explain this difference (Atezolizumab Investigator's Brochure, 2018).

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 AEs (93.0% vs 97.9%, respectively), related Grade 3-4 AEs (40.4% vs 40.6%, respectively), SAEs (28.1% vs 21.5%, respectively), AEs leading to study treatment discontinuation (17.5% vs 15.9%, respectively), and AESIs (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 1.1.2.2, 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 tumour infiltrating lymphocytes (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 (Cancer Discov. 2015). PD-L1 expression is also more prevalent in TNBC than in other breast cancer subtypes (Mittendorf et al. 2014). 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 (Cancer Discov. 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 1.1.2.2 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. To date, the majority of these events have been manageable without requiring treatment discontinuation.

1.3.2 Paclitaxel and Combination Treatment with Atezolizumab

The safety of single-agent paclitaxel in patients with mBC has been demonstrated in several studies; refer to Section 3.3.3.

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 + nab-paclitaxel or paclitaxel in patients with previously untreated NSCLC and is being tested in combination with nab-paclitaxel in patients with TNBC. No exacerbation of

chemotherapy-associated adverse events has been reported to date.

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 paclitaxel 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). Clinical evidence exists to suggest that T-cell and NK-cell functions are enhanced in patients with breast cancer (stage II/III) treated with taxanes compared with patients who did not receive taxanes (Carson et al. 2004). In addition, 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.

Further rationale for the choice of paclitaxel as the comparator and for the selected dose of paclitaxel is provided in Section 3.3.3.

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and PK of atezolizumab plus paclitaxel compared with placebo plus paclitaxel in patients with inoperable locally advanced or metastatic TNBC who have not received prior systemic therapy for these conditions. 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 paclitaxel compared with placebo plus paclitaxel as measured by progression-free survival (PFS)	• PFS, defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause during the study, whichever occurs first. PFS will be tested hierarchically in the following fixed order:
	  • In the subpopulation with programmed death-ligand 1 (PD-L1)-positive tumour status.
	  • In the intent-to-treat (ITT) population.

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by overall survival (OS), 12-month and 18-month OS rates, health-related quality of life (HRQoL), 12-month PFS rate, objective response rate (ORR), duration of objective response (DoR), and clinical benefit rate (CBR)	• OS, defined as the time from randomisation to death from any cause in the PD-L1-positive subpopulation. • OS in the ITT population. • 12-month and 18-month OS rates. • Time to deterioration (TTD) in Global Health Status/HRQoL, defined by a minimally important decrease of ≥ 10 points on the Global Health Status /HRQoL scale (items 29 and 30) of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). • PFS rate at 12 months. • ORR, defined as the percentage of patients with measurable disease at baseline, who have achieved complete response (CR) or partial response (PR), as determined by the investigator using RECIST v1.1. • DoR, defined as the period from the date of initial CR or PR until the date of PD or death from any cause during the study, whichever occurs first. DoR is evaluated in the subset of patients with measurable disease at baseline, who have achieved an objective response. • CBR, defined as the percentage of patients who have achieved CR, PR, or stable disease (SD) that lasts at least 6 months. In addition, as per FDA request, 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).
Exploratory Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by second line PFS (PFS2)	• PFS2, defined as time from randomisation to tumour progression or death from any cause on next line of treatment, whichever occurs first.
• To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab plus paclitaxel compared with placebo plus paclitaxel, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23), using descriptive statistics	• Changes from baseline score in patient function (physical, role, social, emotional, cognitive) and disease/treatment-related symptoms by cycle, and between treatment arms as assessed by all function scales and symptom items/scales of the EORTC QLQ-C30 and QLQ-BR23.
• To evaluate PROs of Global Health Status/HRQoL scale associated with atezolizumab plus paclitaxel compared with placebo plus paclitaxel, as measured by the Global Health Status/HRQoL scale of the EORTC QLQ-C30, using descriptive statistics	• Changes from baseline score in HRQoL by cycle, and between treatment arms as assessed by the Global Health Status/HRQoL scale (items 29 and 30) of the EORTC QLQ-C30.

Objectives	Corresponding Endpoints
• To evaluate and compare between treatment arms patient's health utility as measured by the European Quality of Life 5 Dimension (EQ-5D) questionnaire to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L (5-level version) questionnaire. • European Quality of Life Visual Analogue Scale (EQ-VAS).
• To evaluate the burden of treatment associated with the addition of atezolizumab to paclitaxel, as measured by the GP5 item 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 timepoint by treatment arm for item GP5 from the FACT-G
Specific Efficacy Objectives for patients recruited in China [1]:	
• The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by PFS 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.
Pharmacokinetic Objective:	
• To characterise the PK of atezolizumab when administered concomitantly with paclitaxel • To characterise the PK of paclitaxel when administered concomitantly with atezolizumab	• Serum concentration (C_{min} and C_{max}) of atezolizumab at specified timepoints • Plasma concentration (C_{min} and C_{max}) of paclitaxel at specified timepoints
Safety Objective:	
• To evaluate the safety of atezolizumab plus paclitaxel compared with placebo plus paclitaxel	• Incidence of adverse events (AEs), with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) • Change from baseline in targeted vital signs and physical findings • Change from baseline in targeted clinical laboratory test results
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. For patients who show evidence of immune-mediated toxicity, samples will be collected and tested for anti-nuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA), circulating anti-neutrophil cytoplasmic antibody (s-ANCA), and perinuclear

Objectives	Corresponding Endpoints
	anti-neutrophil cytoplasmic antibody (p-ANCA).
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objective:	
• To assess the activity and safety of atezolizumab according to PD-L1 status	• Relationship between PD-L1 protein expression by immunohistochemistry (Ventana® SP142 assay) in tumour tissues obtained within 3 months prior to patient randomisation [2], and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC 1/2/3).
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 tissues (obtained at baseline/within 3 months prior to randomisation [2], on-treatment, and at disease progression) and blood and their association with disease status and/or response to study drug. • To assess changes in blood- and tissue-based biomarkers during paclitaxel +/- 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 [CD]8) 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 by NGS genotyping in tumour tissues. • 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 paclitaxel +/- atezolizumab treatment. • Correlation of immune biomarker findings in blood and tissue samples from this study to findings from other studies in TNBC and other tumour types.

[1] Applicable only if the China-only recruitment is initiated.

[2] If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent sample should be used.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of the Study Design

This is a Phase III, global, multicentre, randomised, double-blind, two-arm, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab (MPDL3280A, an anti-PD-L1 antibody) administered in combination with paclitaxel compared with placebo in combination with paclitaxel in patients with previously untreated, inoperable locally advanced or metastatic, centrally confirmed TNBC.

Patients will be enrolled in the study globally (Global study), which may be followed by additional enrolment in China only:

- **Global study:** Approximately 600 patients will be randomised at approximately 200 sites globally (in select countries from Europe, Asia/Pacific, as well as North-, and South America). Patients will be randomised centrally, using an interactive voice or web response system (IxRS), in a 2:1 randomisation 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. Randomisation will be stratified by the following factors: tumour PD-L1 status (IC0 vs. IC1/2/3), prior taxane treatment (yes vs. no), presence of liver metastases (yes vs. no), and region (North America vs. Western Europe/Australia; vs. Eastern Europe/Asia Pacific vs. South America). Randomised patients will not be replaced.
- **Additional enrolment in China**: After approximately 600 patients have been randomised in the Global study, global recruitment will be closed. Additional patients may be subsequently randomised in China only, following the same randomisation procedures and ratio (2:1), for a total enrolment of approximately 130 patients in mainland China (including patients 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. Analyses based on the China Population will be performed and summarised separately.

In the absence of disease progression or unacceptable toxicity, study treatment will continue until the end of the study (EOS; defined as last patient last visit, or LPLV). In the absence of disease progression, paclitaxel and atezolizumab/placebo may be discontinued for toxicity independently of each other, with the other treatment being continued. The Sponsor, patients, and investigators will not be aware of the patient's treatment assignment.

In order to evaluate the mechanism of action of the drug combination in the tumour microenvironment, its dependency on PD-L1 expression, changes in blood- and tissue-based biomarkers during treatment, as well as possible resistance mechanisms, paired tumour tissue biopsies will be collected close to the treatment start (mandatory sample), on-treatment (optional sample; collected pre-dose on Cycle 2, Day 1, prior to steroid medication), and at first evidence of radiographic disease progression per RECIST v1.1

(optional sample; collected if clinically feasible from a new or progressing tumour lesion).

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 until disease progression (PD), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. 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. Tumour assessments will be performed on the specified schedule regardless of treatment delays, interruptions or discontinuations. Radiologic imaging performed during the screening period should consist of 1) computerized tomography (CT) and/or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis, 2) bone scan or PET scan, 3) CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis, and 4) any other imaging studies (CT neck, plain films, etc.) as clinically indicated/determined by the treating physician. 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. For each patient, the same radiographic procedures and technique must be used for disease evaluation throughout the study (e.g., the same contrast protocol for CT scans and/or MRI). Evaluation of tumour response (e.g., for estimation of PFS, PFS rate, ORR, DoR and CBR) will be completed per RECIST v1.1. All primary imaging data used for tumour assessment will be collected by the Sponsor to enable centralised, independent review of response endpoints by an Independent Review Committee (IRC) (e.g., to meet potential requests by a reviewing Health Authority).

Patients randomised to either group must discontinue all study treatment upon determination of 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.

All patients who discontinued study treatment before EOS (including due to PD) will be followed for survival approximately every 3 months until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. Information regarding PFS2, PROs and the use of subsequent anti-cancer agents for metastatic TNBC will also be collected during the survival follow-up period. In addition, for patients who discontinue study treatment before EOS for reasons other than PD, tumour assessments will continue until PD, death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor.

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

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

3.1.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor study conduct and review aggregate safety data by treatment arm on a periodic basis. 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 Center (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 Boards/Ethics Committees (IRBs/ECs).

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 EOS is defined as the date when the last patient, last visit (LPLV) is completed.

In addition, the Sponsor may decide to terminate the study at any time.

3.2.1 Global Study

This is an event driven trial. The Global study will end after the required number of events for the final analysis of OS in the PD-L1-positive subpopulation has been reached.

The clinical cut-off (CCO) date for the final OS analysis will be confirmed when the targeted number of mortality events (122 deaths) have occurred in the PD-L1-positive subpopulation globally, which is expected approximately 40 months after the first patient was randomised ("first patient in"; FPI) in the Global study.

The actual length of the study and the time for final analysis will depend on the actual enrolment 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.

3.2.2 China Population

For patients randomised during additional enrolment in China, the study will end when the pre-specified number of 36 PFS events has occurred in the China population with PD-L1-positive tumour status, or when the Global study ends, whichever is later.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for the Atezolizumab Dose and Schedule

Atezolizumab will be administered IV at a flat dose of 840 mg every two weeks (Q2W) to align with the chemotherapy schedule.

The fixed dose of 840 mg administered Q2W was selected with the intent of selecting a dose that is the exposure equivalent of the fixed dose of 1200 mg Q3W (weight-based equivalent of 15 mg/kg), which has been approved for treating patients with metastatic TNBC (in the USA), urothelial carcinoma and NSCLC (refer to the TECENTRIQ™ prescribing information). Of note, the exact equivalent dose is 800 mg; however, because atezolizumab is formulated at a concentration of 60 mg/mL, 800 mg corresponds to a volume of 13.33 mL, and in the interest of simplifying administration, the exact dose used in this study will be 840 mg, corresponding to a volume of 14 mL, which can be accurately administered with a single syringe. The 840 mg dose is not expected to result in meaningfully different exposure compared with the 800 mg dose.

In the Phase Ia Study PCD4989g, patients were treated with doses ranging from 0.1 to 20 mg/kg. Anti-therapeutic antibodies (ADAs) to atezolizumab were associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but not for patients treated at 10, 15, and 20 mg/kg, including the approved dose of 1200 mg. To date, no relationship has been observed between the development of measurable ADAs and safety or efficacy.

3.3.2 Rationale for Patient Population and Analysis Groups

The target population will include patients with previously untreated inoperable locally advanced or metastatic TNBC. Patients will be either newly diagnosed or have disease progression after completing treatment for early breast cancer at least 12 months prior to randomisation.

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). Although TNBC may respond to chemotherapy, including taxanes, 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 TNBC patients 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 TNBC patients could be utilised to modify the course of the disease.

Atezolizumab showed promising anti-tumour activity, as determined by RECIST v1.1 responses, across multiple advanced tumour types (including TNBC) both as monotherapy (Phase 1a study PCD4989g) as well as in combination with bevacizumab and/or chemotherapy (Phase 1b study GP28328). In patients with mTNBC, atezolizumab has shown activity as monotherapy (Emens et al. 2018), and most notably in combination with nab-paclitaxel (Adams et al. 2018; Schmid et al. 2018).

The rationale for performing the primary analysis of PFS in patients with PD-L1-positive tumour status is based on the results of the primary analysis of PFS in the global, randomised, double-blind, phase 3 IMpassion130 study, and specifically on the result in the PD-L1-positive subpopulation (Schmid et al. 2018). Analysis of the co-primary efficacy endpoints (final for PFS, and 1st interim for OS) in the PD-L1-positive population showed that after a median follow-up of 12.9 months, treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel resulted in significantly prolonged PFS (median PFS 7.5 vs. 5.0 months, respectively; HR=0.62, 95% CI: 0.49-0.78, p<0.0001), and longer OS (median OS 25.0 vs 15.5 months, respectively; HR=0.62, 95% CI: 0.45-0.86); due to the pre-specified 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. In addition, in the PD-L1-positive subpopulation, treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel was associated with longer investigator-assessed objective response rate (ORR; 59% vs 43%, respectively; treatment difference 16%, p=0.0016), and median duration of response (8.5 months vs 5.5 months, respectively) (Schmid et al. 2018).

Driven by the results of the interim analysis of the IMpassion130 study, the Sponsor, in consultation with the Steering Committee, has decided to amend the primary analysis of the MO39196 (IMpassion131) study to include PFS by RECIST v1.1 in the PD-L1-positive subpopulation (analysed first), while retaining PFS by RECIST v1.1 in the intent-to-treat (ITT) population (analysed second). In addition, stratified analyses of PFS will be completed according to predefined and clinically important randomisation stratification factors, including tumour PD-L1 status (PD-L1-negative subpopulation, defined as IC0 at the time of randomisation vs. PD-L1-positive subpopulation, defined as IC1/2/3 at the time of randomisation), prior taxane treatment (yes vs. no) and presence of liver metastases (yes vs. no). Analysis of the relationship between PD-L1 status by IHC in tumour tissues obtained prior to patient randomisation, and clinical efficacy and safety outcomes is a predefined biomarker objective of the study.

3.3.3 Rationale for Concomitant Paclitaxel Treatment

The taxane class of cytotoxic agents (paclitaxel, docetaxel, nab-paclitaxel) have significant anti-tumour activity in breast cancer. 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 taxane-based 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).

Several studies and meta-analyses support the benefit of taxanes on clinical outcomes in mBC (Piccart-Gebhart et al. 2008; Qi et al. 2013; Ghersi et al. 2015), and these benefits were generally comparable to those of anthracyclines in randomised controlled clinical studies. However, in a recent meta-analysis of 28 studies (N= 6871 randomised women), the combined hazard ratio (HR) for OS and time to progression (TTP) favoured the taxane-containing compared to the anthracycline regimens (HR 0.93, 95% CI 0.88 to 0.99, P = 0.002, deaths = 4477; and HR 0.92, 95% CI 0.87 to 0.97, P = 0.002, estimated 5122 events, respectively). When the analyses were restricted to first-line treatments, this effect persisted for OS (HR 0.93, 95% CI 0.87 to 0.99, P = 0.03) but not for TTP. Tumour response rates were higher with taxane-containing chemotherapy in assessable women (RR 1.20, 95% CI 1.14 to 1.27, P < 0.00001). Taxanes were also associated with an increased risk of neurotoxicity but less nausea and vomiting compared to non-taxane-containing regimens (Ghersi et al. 2015).

Although combinations of cytotoxic agents may be administered to patients with severe symptomatic disease or imminent visceral crisis, these combination regimens are associated with increased toxicity (Piccart-Gebhart et al. 2008; Greene and Hennessy 2015), which underscores the need for combination regimens in which adding a targeted therapy to a cytotoxic agent does not result in enhanced or cumulative toxicity.

Paclitaxel, docetaxel, and nab-paclitaxel are approved drugs for the treatment of recurrent and metastatic BC in many countries. Paclitaxel is administered weekly (80 - 90 mg/m^2) (Swanton 2011) or every three weeks (175 mg/m^2 dose recommended by the current Prescribing Information for Taxol® IV injection), with weekly paclitaxel (80–90mg/m^2) currently considered the most effective schedule for delivering paclitaxel (Swanton 2011). A meta-analysis of 11 randomised clinical trials (n=2,540 patients) comparing weekly- and three-weekly taxanes in patients with advanced BC found that weekly administration of paclitaxel resulted in higher OS compared to the three-weekly schedule (HR 0.78; 95% CI, 0.67–0.89 P=0.001); PFS was similar between the two schedules. The incidence of serious adverse events, neutropoenia, neutropoenic fever, and peripheral neuropathy were also significantly lower with the weekly compared to the three-weekly taxane schedules (Mauri et al. 2010). In addition, a regimen consisting of weekly paclitaxel administrations for three weeks, followed by one-week break was reported to be associated with less neurotoxicity compared to continuous weekly administrations (Swanton 2011). This finding is consistent with the lower neurotoxicity rate observed in the HER2-negative mBC population of the studies E2100 (Miller et al. 2007) and MERIDIAN (Miles et al. 2017), both using a 90 mg/m^2 3-week on/1-week off weekly paclitaxel schedule, compared to study CALGB9840 (Seidman et al. 2008) using continuous 80 mg/m^2 weekly paclitaxel dosing without interruption. Taken together, these findings support the selected regimen for paclitaxel (90 mg/m^2 on days 1, 8, and 15 of every 28-day cycle) in the current study.

The solvents used to enhance the solubility of taxanes have been associated with allergic reactions and peripheral neuropathy (ten Tije et al. 2003). Therefore, to reduce

the risk of severe hypersensitivity reactions, study patients should be premedicated as described in Section 4.4.1.1.

3.3.4 Rationale for the 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. In the current study, all randomised patients will receive paclitaxel, a standard treatment for mTNBC; refer to Section 3.3.3.

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 characterisation 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). The correlation between PD-L1 expression and atezolizumab activity in TNBC is not well established yet. However, it is possible that not all patients may equally benefit from treatment with atezolizumab. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond to atezolizumab. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

3.3.5.1 Rationale for 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 within 3 months prior to randomisation. If a tumour sample taken within 3 months before randomisation 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. Tumour specimens should be formalin-fixed paraffin-embedded (FFPE) (preferred; alternatively, at least 17 unstained slides are required to participate in this study. Slides must be of good quality (based on total and viable tumour content), with an associated pathology report. These tumour specimens will also be used for retrospective confirmation of HER2, ER, PR expression by a central testing laboratory. If multiple tumour specimens are submitted, at least one specimen must be evaluable for

PD-L1, to allow for stratification based on tumour PD L1 expression as determined by IHC (IC0 vs. IC1/2/3) at randomisation.

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

3.3.5.2 Rationale for 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 ribonucleic acid [RNA] sequencing) from these specimens will help elucidate molecular changes associated with resistance to or disease progression after treatment with paclitaxel plus atezolizumab or paclitaxel plus placebo in patients with TNBC.

3.3.5.3 Rationale for the Optional On-treatment Biopsy Specimen Collection

One optional on-treatment tumour sample will be collected (if clinically feasible) 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 paclitaxel plus atezolizumab compared to paclitaxel 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.

3.3.5.4 Rationale for Blood Sampling for Biomarkers

Changes in different blood biomarkers may provide evidence for biologic activity of atezolizumab in combination with paclitaxel in humans and may allow for the development of a blood-based biomarker to help predict which patients may benefit from atezolizumab plus paclitaxel. 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.

3.3.6 Rationale for Patient-Reported Outcome Assessments

As mBC is not curable with currently approved and available therapies, the main goals of treatment are to prolong survival and maintain or improve quality of life (Cardoso et al. 2012). Patient-reported outcomes (PROs) of global health status, function, and disease/treatment related symptoms will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) in conjunction with its QLQ-BR23 breast cancer module, as well as the European Quality of Life 5 Dimension, 5-level version (EQ-5D-5L) questionnaire (see Section 4.5.8 for further details and Appendix 4 for a sample of each instrument).

The EORTC QLQ-C30 and QLQ-BR23 instruments are validated and reliable self-report measures (Aaronson et al.1993; Sprangers et al. 1996; Osoba et al. 1997; Osoba et al. 1998). The EQ-5D-5L is a validated, generalised HRQoL measure that assesses patient's health status related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). A utility measure is obtained that is used to inform pharmacoeconomic evaluations.

As the QLQ BR23 was not developed or tested and validated in men, male patients in this study will not complete the QLQ-BR23 questionnaire.

3.3.7 Rationale for the Adverse Event Reporting Period

The reporting period in this study is defined as 30 days after the last dose of atezolizumab/placebo for adverse events, and 90 days after the last dose of atezolizumab/placebo for serious adverse events (SAEs) or adverse events of special interest (AESI). The rationale for this reporting period (as opposed to five half-lives of atezolizumab, or five months) is based on a review of adverse events occurring >30 days after the last dose of atezolizumab in Study PCD4989g, which revealed no long-term safety concerns. Approximately 92 of 443 treated patients (21%) in Study PCD4989g reported adverse events between 31 and 90 days after last dose of atezolizumab; of these, 38 patients (9%) reported events related to disease progression. Adverse events reported by the remainder of patients were mainly single occurrences of a broad range of event terms with no pattern or trend for any System Organ Class (SOC) or type of event. These events were considered indicative of the patients' underlying cancer and were not representative of delayed toxicity related to atezolizumab. Therefore, the Sponsor considers the collection of all adverse event data until 30 days after the last dose of the study drug, and for 90 days after the last dose for SAEs and adverse events of special interest to be sufficient for the on-going assessment and characterisation of the overall safety profile for atezolizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population will include patients with previously untreated inoperable locally advanced or metastatic TNBC. Patients will be either newly diagnosed or have disease progression after completing treatment for early breast cancer at least 12 months prior to randomisation. The enrolment criteria will be identical for all patients (global and additional enrolment in China).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Women or men aged ≥18 years
3. Patients with locally advanced or metastatic, histologically documented TNBC (absence of human epidermal growth factor 2 [HER2], oestrogen receptor [ER], and progesterone receptor [PR] expression), not amenable to surgical therapy.

a) HER2 negativity is defined as either of the following: IHC 0, IHC 1+ or IHC2+/*in situ* hybridisation (ISH)- as per American Society of Clinical Oncology (ASCO)-College of American Pathologists Guideline (CAP) guideline (ISH- is defined as a ratio of HER2 to CEP17 <2.0) (Wolff et al. 2018).
b) ER and PR negativity are defined as <1% of cells expressing hormonal receptors via IHC analysis as per ASCO-CAP guideline (Hammond et al. 2010).

4. Eligible for taxane monotherapy.
5. No prior chemotherapy or targeted systemic therapy (including endocrine therapy) for inoperable locally advanced or metastatic TNBC.

   Prior radiation therapy for metastatic 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.

   Previous chemotherapy for early breast cancer (eBC; neoadjuvant or adjuvant setting) is permitted if completed ≥12 months before randomisation.

   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.
6. Availability of formalin-fixed paraffin-embedded (FFPE) tumour block (preferred) or at least 17 unstained slides, collected ≤3 months prior to randomisation, with an associated pathology report, if available. If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent 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 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 for PD-L1 testing, and the score measured in the most recent sample prior to enrolment will be used as the PD-L1 score for patient stratification.
      i. Acceptable samples include core needle biopsies for deep tumour tissue (more than one core if clinically feasible) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
      ii. Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are <u>not</u> acceptable.
      iii. Tumour tissue from bone metastases is not evaluable for PD-L1 expression and is therefore <u>not</u> acceptable.
7. ECOG performance status of 0 or 1
8. Life expectancy ≥ 12 weeks

9. Measurable disease, as defined by RECIST v1.1. (Note: Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.)
10. Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment (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 Cycle 1, Day 1)
    b. Lymphocyte count ≥ 500/μL
    c. Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
    d. Haemoglobin ≥ 9.0 g/dL

       Patients may be transfused or receive erythropoietic treatment to meet this criterion.
    e. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5× the upper limit of normal (ULN), with the following exceptions:
        i. Patients with documented liver metastases: AST and ALT ≤ 5× ULN
        ii. Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5× ULN
    f. Serum bilirubin ≤ 1.25× ULN

       Patients with known Gilbert's disease who have serum bilirubin level ≤ 3× ULN may be enrolled.
    g. International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5× ULN

       This applies only to patients who are not receiving an anticoagulant medicinal product; patients receiving an anticoagulant medicinal product should be on a stable dose and have an INR which is not above the target therapeutic range.
    h. Calculated creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault).
11. Negative human immunodeficiency virus (HIV) test at screening.
12. Negative hepatitis B surface antigen (HBsAg) test at screening.
13. 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 positive HBcAb test.
14. 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 a positive HCV antibody test.

15. Women of child bearing potential must agree to either use a contraceptive method with a failure rate of ≤ 1% per year or to remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 5 months after the last dose of atezolizumab/placebo, or for at least 6 months after the last dose of paclitaxel.

    A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilisation (removal of ovaries and/or uterus).

    Examples of contraceptive methods with a failure rate of ≤ 1% per year include bilateral tubal ligation, male sterilisation, 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 acceptable methods of contraception.

16. Women of child bearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.

17. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

    a. 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 6 months after the last dose of paclitaxel. Men must refrain from donating sperm during this same period.

    b. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study 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.

4.1.2 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 at least 2 weeks prior to randomisation.

2. Known central nervous system (CNS) disease, except for treated asymptomatic CNS metastases, provided all of the following criteria are met:

    a. Measurable disease outside the CNS

    b. Metastases are limited solely to cerebellar and supratentorial lesions (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

c. No ongoing requirement for corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed)

d. No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomisation

e. No evidence of progression or haemorrhage after completion of CNS directed therapy

Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible, if all other criteria above are met.

3. Leptomeningeal disease
4. Uncontrolled pleural effusion, pericardial effusion, or ascites (Note: patients with indwelling catheters, such as PleurX® are allowed)
5. Uncontrolled tumour-related pain

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

    b. 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. There is no required minimum recovery period.

    c. 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.

6. Uncontrolled hypercalcemia (>1.5 mmol/L [>6 mg/dL] ionized calcium or serum calcium [uncorrected for albumin] >3 mmol/L [>12 mg/dL] or corrected serum calcium >ULN) or clinically significant (symptomatic) hypercalcemia

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

7. Malignancies other than TNBC within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer).

<u>General Medical Exclusion Criteria</u>

8. Pregnant or lactating women, or intending to become pregnant during the study.
9. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome).

10. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomisation, unstable arrhythmias, or unstable angina.
    a. Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.
    b. 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 optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
11. Presence of an abnormal electrocardiogram (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.
12. Serious infection requiring antibiotics within 2 weeks prior to randomisation, including but not limited to infections requiring hospitalisation or IV antibiotics, such as bacteraemia, or severe pneumonia.
13. Major surgical procedure within 4 weeks prior to randomisation or anticipation of the need for a major surgical procedure during the study other than for diagnosis. Note: 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 30 days prior to initiation of study treatment.
15. Inability to understand the local language(s) for which the Patient Reported Outcome (PRO) questionnaires are available.

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

16. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
17. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells or any component of the atezolizumab formulation
18. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis (MS), vasculitis, or glomerulonephritis. (Note: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.)
19. Prior allogeneic stem cell or solid organ transplantation
20. History of idiopathic pulmonary fibrosis (IPF, including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic

organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan. (Note: History of radiation pneumonitis in the radiation field [fibrosis] is permitted.)

21. Current treatment with anti-viral therapy for HBV.
22. Active tuberculosis
23. Receipt of a live, attenuated vaccine within 4 weeks prior to randomisation or anticipation that such a live, attenuated vaccine will be required during the study.

    Note: Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to randomisation, during treatment or within 5 months following the last dose of atezolizumab/placebo.
24. Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or immune checkpoint 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 immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to randomisation, or anticipated requirement for systemic immunosuppressive medications during the trial.
    a. Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.
    b. Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumour assessments performed using MRI.
    c. The use of corticosteroids (≤ 10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
    d. Systemic corticosteroids are allowed as paclitaxel premedication during the trial at a dose ≤10 mg dexamethasone or equivalent in order to avoid severe hypersensitivity reactions.
27. Poor peripheral venous access
28. Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
29. Any other serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study.

Exclusion Criteria Related to Paclitaxel

30. History of hypersensitivity reactions to paclitaxel or other drugs formulated in the same solvent as paclitaxel (polyoxyethylated castor oil).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the IxRS (ALMAC Clinical Technologies) for eligible patients.

Randomisation to atezolizumab plus paclitaxel or placebo plus paclitaxel will occur in a 2:1 ratio, using a permuted-block randomisation method. 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:

- Tumour PD-L1 status (IC0 vs. IC1/2/3)
- Prior taxane treatment (yes vs. no), and
- Presence of liver metastases (yes vs. no)
- Region (North America vs. Western Europe/Australia; vs. Eastern Europe/Asia Pacific vs. South America).

Patients should receive their first dose of study treatment on the day of randomisation, if possible. If this is not possible, the first dose should occur no later than 3 days after randomisation.

With the exception of stratifying by region, the same randomisation method and ratio (2:1) will be implemented for the China only patients.

The Sponsor and its agents (with the exception of 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); the study site personnel, including the investigator; and the patient will be blinded to treatment assignment prior to unblinding of the treatment assignment at the study level; refer to Section 4.2.1. While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this trial. Therefore, Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analysed. Samples from patients assigned to the comparator arm will not be analysed except by request (e.g., to evaluate a possible error in dosing).

The Sponsor and its agents (except for the PD-L1 assay provider and members of the iDCC and iDMC), the study site personnel, including the investigators, and the patients will be blinded to PD-L1 status prior to unblinding of the treatment assignment at the study level; refer to Section 4.2.1.

4.2.1 Unblinding

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

Unblinding of treatment assignment may only occur under the following circumstances.

4.2.1.1 Emergency Unblinding

Per health authority reporting requirements, treatment assignment will be unblinded for serious, unexpected study drug-related toxicity (e.g., as part of the Investigational New Drug [IND] safety reporting process). In these instances, investigators will not be notified of individual patient's treatment assignment as a matter of course.

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. Investigators are encouraged to consult with the Medical Monitor prior to performing emergency unblinding. If unblinding is necessary for patient safety management, the investigator is authorised to break the treatment code within the IxRS solely for the patient experiencing the treatment emergent adverse event by using a personal identification (PIN) code which is issued to them at the start of the study.

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.

4.2.1.2 Unblinding upon Disease Progression

Prior to disease progression, patients' 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 a 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 that the patient meets the eligibility 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 eligibility for the next-line approved treatment or clinical trial;
- 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. Approval of the request and unblinding of study drug assignment under this scenario will occur only during business hours. The Sponsor will not be informed of the patient's treatment allocation at the time of unblinding.

Crossover to atezolizumab for patients allocated to placebo is not allowed upon unblinding.

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

4.2.1.3 Unblinding at the Study Level

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

4.3 STUDY TREATMENT

Atezolizumab/placebo and paclitaxel are considered investigational medicinal products (IMPs) in this study. 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 4.4.1.2), and other permitted concomitant medications (see Section 4.4.1.3).

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 and paclitaxel).

4.3.1 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, 20cc 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 (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% 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 be supplied by the Sponsor.

Placebo will consist of the vehicle without the antibody. Placebo will be supplied in a single-use, 20cc USP/Ph. Eur. Type 1 glass vial as a colourless, 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 Paclitaxel

Paclitaxel is considered standard of care in patients with TNBC. However, the paclitaxel dosing regimen used in this study (90 mg/m^2 via IV infusion on Days 1, 8, and 15 of every 28-day cycle) is not approved in patients with TNBC. Therefore, paclitaxel will be considered an IMP in this study, and provided by the Sponsor. For information on the formulation, packaging, and handling of paclitaxel, refer to the local prescribing information for paclitaxel.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab/Placebo

Patients will receive atezolizumab 840 mg (corresponding to 14 mL from drug product, in 250 mL 0.9% sodium chloride [NaCl]) or matching placebo by IV infusion administered on Day 1 and Day 15 (± 3 days) of every 28-day cycle. 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.

Administration of atezolizumab or placebo will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Atezolizumab/placebo infusions will be administered per the instructions outlined in Table 3.

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 14 mL atezolizumab (840 mg) in 250 mL NaCl) over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated • 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 and after the infusion if clinically indicated. • 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 and after the infusion if clinically indicated.

Patients randomised to either group must discontinue all study treatment upon determination of 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 EOS.

Dose reduction of atezolizumab/placebo is not permitted. Atezolizumab/placebo and paclitaxel may be discontinued for toxicity independently of each other in the absence of PD. Guidelines for management of specific adverse events and for atezolizumab/placebo dosing interruption or discontinuation are provided in Section 5.1.4 and Section 5.1.5.3.1, respectively.

There is currently no information on overdose with atezolizumab. Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Paclitaxel

Paclitaxel will be administered at the 90 mg/m^2 dose via 1-hour IV infusion on Days 1, 8,

and 15 of every 28-day cycle. On days of scheduled infusions of atezolizumab/placebo and paclitaxel (i.e., Day 1 and Day 15 of every cycle), paclitaxel is to be administered after infusion of atezolizumab/placebo. Doses of paclitaxel should not be administered more frequently than every 7 days.

In the absence of unacceptable toxicity, paclitaxel will be administered until PD or until the end of the study, whichever occurs earlier. Paclitaxel and atezolizumab/placebo may be discontinued for toxicity independently of each other in the absence of disease progression.

To reduce the risk of severe hypersensitivity reactions, study patients will be premedicated as described in Section 4.4.1.1.

Sites should follow their institutional standard of care for determining the paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

Guidelines for paclitaxel dosage modification and treatment interruption or discontinuation due to toxicity are provided in Section 5.1.5.3.2.

Any overdose or incorrect administration of paclitaxel should be noted on the Paclitaxel Administration eCRF. Adverse events associated with an overdose or incorrect administration of paclitaxel should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab/placebo and paclitaxel) will be provided by the Sponsor. 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.

Unused 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 destruction of any unused IMP must be agreed to by the Sponsor. The site must obtain written authorisation from the Sponsor before any 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.

4.3.4 Post-Trial Access to Atezolizumab

The Sponsor will offer post-trial access to the 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** the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued atezolizumab 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
- The patient was assigned to atezolizumab treatment at study randomisation.

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 atezolizumab or data suggest that atezolizumab is not effective for mTNBC
- The Sponsor has reasonable safety concerns regarding atezolizumab as treatment for mTNBC
- The patient was assigned to placebo treatment at study randomisation.

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 includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient 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 EOS visit, only new anti-cancer treatment will be recorded.

4.4.1 Permitted Therapy

4.4.1.1 Premedication

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.

To reduce the risk of severe hypersensitivity reactions, all patients should be premedicated prior to paclitaxel administration. Prior to receiving the first two study infusions of paclitaxel, all patients will receive corticosteroids (8-10 mg dexamethasone or equivalent) as part of either the institutional standard of care or the following premedication:

- Dexamethasone 8-10 mg (or equivalent) administered orally approximately 12 and 6 hours prior to the paclitaxel infusion

  Patients may be treated with dexamethasone ≤10 mg IV within 1 hour prior to the paclitaxel infusion if the patient did not take the oral dexamethasone.
- Diphenhydramine 50 mg IV (or equivalent) 30-60 minutes prior to the paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30-60 minutes prior to paclitaxel infusion.

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 to the extent that is clinically feasible. For example, if paclitaxel is well tolerated during the first two weekly infusions without apparent hypersensitivity reaction, a reduction in the dose of dexamethasone premedication (or equivalent) should be considered for subsequent cycles if permitted by institutional standard of care. This approach has been reported to be successful in the literature (Berger et al. 2012).

4.4.1.2 Treatment of Infusional Adverse Events

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine (or equivalent substitutes, per local practice), and/or famotidine or another H_2 receptor antagonist, per 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).

4.4.1.3 Other Permitted Therapy

The following therapies are permitted on study:

- Prophylactic or therapeutic anticoagulation therapy (such as low–molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumour target lesions. Candidate lesions for radiotherapy must be decided prior to study entry.

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

- Inactivated vaccinations (including for influenza)
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids (≤10 mg prednisone equivalent per day) for patients with orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for the prevention of skeletal events
- 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.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per local standards.

Patients who use contraceptives should continue their use during the treatment period and for at least 5 months after the last dose of study treatment; refer to Section 4.1.1.

4.4.2 Prohibited and Cautionary Therapy

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.

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 five 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 4.

Table 4 Prohibited Medications and Treatments

Prohibited Medication/Class	Minimum Washout Period Prior to Randomisation
Any other systemic anti-cancer therapy	28 days or five half-lives of the drug (whichever is longer)
Any investigational therapy	30 days
Immunomodulatory agents, e.g., interferons or IL 2 [1]	28 days or five half-lives of the drug (whichever is longer)
Immunosuppressive medications, e.g., cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide [2]	14 days
Corticosteroids as therapy for CNS disease	1 day
Any live, attenuated vaccine (e.g., FluMist®) [3]	28 days
Stereotactic radiation for CNS metastases Whole-brain radiation for CNS metastases	7 days 14 days

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

[2] These agents could potentially alter the activity and the safety of atezolizumab.

[3] 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 and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids 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 and TNF-α inhibitors may be administered at the discretion of the treating physician.

Systemic corticosteroids are recommended, with caution 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.

The concomitant use of herbal therapies is not recommended, as their PK, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator.

4.4.3 Additional Restrictions Related to Paclitaxel

The metabolism of paclitaxel is catalysed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. The PK of paclitaxel was shown to be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. Therefore, caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir,

ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Granulocyte-colony stimulating factor (G-CSF) as haematopoietic support is permitted for patients receiving paclitaxel. The primary prophylaxis should be administered per the ASCO, EORTC, and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who have an approximately 20% or higher risk for febrile neutropoenia based on patient-, disease- and treatment-related factors, such as age ≥ 65 years, previous chemotherapy or radiation therapy, preexisting neutropoenia or bone marrow involvement, infection, comorbidities, etc. (Smith et al. 2015; Aapro et al. 2011; Crawford et al. 2009).

Consistent with the latest ASCO recommendations (Smith et al. 2015), and results of meta-analyses of primary G-CSFs in adults undergoing chemotherapy for a solid tumour or lymphoma (Pinto et al. 2007; Cooper et al. 2011; Renner et al. 2012), both conventional (e.g., filgrastim) and long-acting, or pegylated (e.g., pegfilgrastim) G-CSFs may be used for the prevention of treatment-related febrile neutropoenia. The choice of agent will be at the discretion of the investigator, depending on the clinical situation and institutional standard of care practice.

Anti-emetics, anti-allergic measures, and other treatments for concomitant paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the local prescribing information for paclitaxel.

Refer to the local prescribing information (label) for paclitaxel for all boxed warnings and contraindications.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures or evaluations. Informed Consent Forms for enrolled patients and for patients who are screening failures 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.

4.5.2 Medical History and Demographic Data

General medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol, and drugs of abuse. 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 screening will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. 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.

At all clinic visits where study treatment is administered, vital signs should be determined within 60 minutes before the first infusion. Vital signs will also be determined during and after the infusions if clinically indicated (see Table 3).

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 disease progression (PD), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. All sites of measurable and non-measurable disease 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 computerized tomography (CT) scans (with oral/IV contrast unless contraindicated) and/or magnetic resonance imaging (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 should 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 evaluation of tumour response per RECIST v1.1 (see Appendix 3) will be performed according to the schedule specified in Appendix 1, regardless of treatment delays, interruptions or discontinuations.

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 magnetic resonance imaging [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, computed tomography (CT) scans, and other modalities, per RECIST v1.1 (see Appendix 3). All primary imaging data used for tumour assessment will be collected by the Sponsor to enable centralised, independent review of response endpoints by an Independent Review Committee (IRC) (e.g., to meet potential requests by a reviewing Health Authority).

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 PD 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: blood urea nitrogen (BUN) or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, total protein, and albumin. Bicarbonates should only be tested at sites where this test is part of the standard safety laboratory panel.

  The Cockcroft-Gault formula (see Appendix 8) will be used to calculate creatinine clearance. Patients must have a CrCl ≥ 30 mL/min to be eligible for enrolment.

  Levels of magnesium and phosphorus must be tested during screening. During treatment, levels of magnesium and phosphorus should be tested as clinically indicated.
- Coagulation panel: activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR); performed at screening/baseline and at treatment discontinuation.
- Serum pregnancy test for women of childbearing potential at screening/baseline (within 7 days prior to initiation of study drug); after randomisation, urine pregnancy tests will be performed at each cycle during treatment and at treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilisation (removal of ovaries and/or uterus).
- Thyroid function testing: thyroid-stimulating hormone (TSH), free T3 (or total T3 for sites where free T3 is not performed), free T4; performed at screening, on Day 1 of Cycle 1, every second cycle thereafter, and at treatment discontinuation.
- Urinalysis: specific gravity, pH, glucose, protein, ketones, and blood; performed at screening, and thereafter only if clinically indicated.

In addition, all patients will be tested for HIV antibody, HBsAg, hepatitis B surface antibody (HBsAb), total hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb) locally during screening. HIV-positive patients will be excluded from the clinical trial. In patients with a negative HBsAg and positive HBcAb serology, HBV DNA must

also be collected prior to randomisation. Patients positive for HCVAb require a negative PCR for HCV RNA to confirm eligibility.

All laboratory tests results must be available for the Investigator's review before treatment administration.

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., ADA 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 C-reactive protein

Samples for C-reactive protein (CRP) assessment will be obtained at screening/baseline, and on Day 1 of each treatment cycle.

4.5.6.2.2 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 collected from patients enrolled in the Global Study 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 utilise a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterise 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 characterisation assays will depend on the safety profile and clinical immunogenicity data.

Patients enrolled in mainland China will not undergo ADA assessments.

4.5.6.2.3 Pharmacokinetic Testing

Samples for atezolizumab PK will be collected from patients enrolled in the Global Study at specific timepoints (see Appendix 2) during the first four cycles of atezolizumab/placebo and at the Treatment discontinuation visit. Serum samples will be assayed for atezolizumab concentrations using a validated immunoassay.

Samples for paclitaxel PK were collected from the first approximately 60 patients randomised in the Global Study (approximately 30 patients in each treatment arm). No further sampling for paclitaxel PK will occur in the study. Plasma samples will be assayed for paclitaxel concentrations using validated methods.

Patients enrolled in mainland China will not undergo atezolizumab PK and paclitaxel PK assessments.

4.5.6.2.4 Auto-antibody Testing

Auto-antibody testing will include anti-double-stranded DNA (anti-dsDNA), circulating anti-neutrophil cytoplasmic antibody (c-ANCA), and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) assays. Baseline samples will be collected on Cycle 1, Day 1 prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected, and all samples will be analysed centrally.

4.5.6.2.5 Biomarker Assays

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 processed to assess peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA and DNA).

Table 5 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarkers
Plasma	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)	Baseline	• Germline DNA as a reference for analysis of somatic gene alterations
ctDNA isolated from plasma	Pre-dose at day 1 of cycles 1, 2 and 3, thereafter every 3 months during treatment and at disease progression	• ctDNA
Whole blood for exploratory biomarker analysis (Peripheral blood mononuclear cells) [1]	Pre-dose at day 1 of cycles 1 and 2, and at disease progression	• Immune cell characterisation
Tumour tissue (mandatory)	Within 3 months before randomisation into the study or at baseline [2]	• PD-L1 (e.g. stratification factor), HER2, ER, PR (e.g. retrospective central confirmation of TNBC) • TILs • Immune-related proteins such as CD8, CD3, FoxP3, CD68 and others
Tumour tissue (optional)	On-treatment biopsy pre-dose at day 1 of Cycle 2, prior to steroid medication (or within 14 days before the Cycle 2, Day 1 dose) (optional) and at time of radiographic progression (or within ±7 days) (optional; preferably from a new or progressing lesion)	• TILs • Immune-related proteins, such as CD8, CD3, FoxP3, CD68 and PD-L1 and others
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

ctDNA: circulating tumour deoxyribonucleic acid; DNA: deoxyribonucleic acid; FoxP3: Forkhead Box P3 protein (scurfin); PD-L1: programmed death ligand 1; RNA: ribonucleic acid; TILs: tumour-infiltrating-lymphocytes; TNBC: triple-negative breast cancer

[1] Whole blood samples for PBMC analysis have been collected from over 300 patients at baseline; for these patients, sample collection will continue as described in Appendix 2 (on Cycle 2, Day 1 and at PD). However, for newly enrolled patients, there will be no whole blood sampling for PBMC analysis at any time-point.

[2] If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent sample should be used.

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

4.5.6.2.6 Collection of Tumour Tissue Samples

Tumour tissue samples will be collected prior to randomisation for eligibility (mandatory), as well as on-treatment and at tumour progression (optional).

Paired tumour tissue biopsies are sought to be collected close to the time of treatment start (mandatory specimen obtained from relapsed metastatic or locally advanced tumour or, if clinically not feasible, from primary surgical resection sample or the most recent FFPE tumour biopsy sample or the most recent FFPE tumour biopsy sample) and on-treatment (optional sample; collected pre-dose on Cycle 2, Day 1, prior to steroid medication, or within 14 days before the Cycle 2, Day 1 dose) to assess changes in the immune tumour-microenvironment by exploratory immune-related biomarker analysis.

Representative formalin-fixed paraffin-embedded (FFPE) tumour specimen blocks (preferred) or at least 17 unstained slides, with an associated pathology report, must be submitted for centralised determination of PD-L1 status prior to study enrolment, and retrospective confirmation of TNBC by HER2, ER and PR staining. If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent sample should be used. Acceptable tumour sample collection methods include core needle biopsies for deep tumour tissue (more than one core if clinically feasible), 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.

A diagnostic antihuman PD-L1 monoclonal antibody (VENTANA SP142) will be used to stain prospectively for PD-L1 expression on formalin-fixed paraffin-embedded tumour tissue by immunohistochemistry (IHC), as described in published literature (Herbst et al. 2014; Powles et al. 2014). 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 whose tumour tissue is not evaluable for prospective central testing are not eligible. If multiple tumour specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1 staining.

In the cadre of the exploratory biomarker objective, the status of immune-mediated 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.

Tissue samples from patients who are not eligible to enrol into the study will be returned no later than 6 weeks after eligibility determination.

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. 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.

4.5.6.3 Use and Storage of Remaining Samples from Other Procedures

4.5.6.3.1 Remaining Samples from Study Procedures

Any remainder blood and tissue samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples in the RBR for future research (see Section 4.5.9), the samples will be stored until no longer needed or used up.

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.

4.5.6.3.2 Remaining Samples from Non-Study Procedures

If a patient undergoes a medically indicated procedure (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy, etc.) any time during the study that has the likelihood of yielding tumour tissue, any remaining samples or a portion of the sample not necessary for medical diagnosis (body fluid samples or leftover tumour tissue) may be used for exploratory analysis in the study. Patients must provide specific consent in order to obtain discarded samples from routine care.

4.5.7 Electrocardiograms

A 12-lead ECG recording will be obtained at screening, and may be obtained at unscheduled time-points during study treatment, as clinically indicated; see Appendix 1. ECGs should be performed prior to other procedures scheduled at that same time (e.g., blood draws). ECG recordings must be obtained after the patient has been resting in a supine position for at least 10 minutes.

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 clinically significant morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Patient-Reported Outcomes

PROs of global health status, function, and disease/treatment related symptoms will be assessed using the EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L, and Functional Assessment of Cancer Therapy – General (FACT-G) questionnaires, to characterise the clinical profile of atezolizumab plus paclitaxel compared to placebo plus paclitaxel. A copy of the PRO instruments is provided in Appendix 4.

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 global HRQoL, including five aspects of patient functioning (physical, emotional, role, cognitive, and social); three symptom scales (fatigue, nausea and vomiting, and pain); and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) with a recall period of “the last week”. Scale scores can be obtained for the multi-item scales. 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 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 will be utilised in this study for economic modelling.

The Functional Assessment of Cancer Therapy – General (FACT-G) is a validated, 27-item, general quality of life instrument comprised of four domains (physical, social/family, emotional, and functional well-being) (Cella et al. 1993). Each item is scored on a five-point scale from 0 (not at all) to 4 (very much). In this study, the burden of treatment associated with the addition of atezolizumab to paclitaxel will be measured by the GP5 item ("I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G instrument. Since item GP5 specifically assesses patients being bothered by the side-effects of treatment, this item will not be administered to patients at baseline.

The PRO instruments (EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L and VAS, and FACT-G) will be completed by the patient on an electronic PRO (ePRO) device at baseline (Cycle 1, Day 1), on Day 1 of each subsequent cycle, and at the treatment discontinuation visit (30 ± 5 days after the last dose of study drug). In addition, all patients will be asked to complete the PRO questionnaires every 3 months for 1 year

after treatment discontinuation, regardless of whether the patient is receiving subsequent anti-cancer therapy. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires must be completed by the patient on the day of the clinic visit either at their home or at the site at the start of the visit, and prior to other study assessments and before administration of study treatment. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff if the patient is unable to complete the measure on their own. Study personnel should review the ePRO device and ensure that all measures have been completed and saved before the patient leaves the investigational site.

The electronic device will be provided by the sponsor together with instructions for completing the questionnaires electronically, which patients will be trained on by the investigator staff. The data will be transmitted to a centralised database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

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 specimens will be used to achieve 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
- 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 and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (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 samples will be stored optionally 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 FFPE tissue and plasma, whole blood samples and derivatives thereof (e.g. RNA, DNA).

Samples may be sent to one or more laboratories to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing (NGS), or other genomic analysis methods, such as RNA expression analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterisation of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analysed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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 Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9.4 Confidentiality

Specimens 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 Informed Consent Form (or separate authorisation 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, data derived from RBR 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 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 Informed Consent Form 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 specimens 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 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 specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF.

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

The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MO39196 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 MO39196.

4.5.9.7 Monitoring and Oversight

RBR specimens 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 Informed Consent Form. 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.

4.5.10 Patient Engagement Application

The Patient Engagement Application, a smartphone app, is an optional service that subjects can opt-in to use in the MO39196 study. The App supports study activities like when to take medication and attend site visits, helping patient compliance. It also provides study specific information on procedures, and can help patients track their own goals too. Available for both iOS and Android devices, the study coordinator will guide

interested participants on using this supporting technology. Additional details are found in Appendix 10.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Withdrawal

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.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Drug Discontinuation

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

- Intolerable toxicity related to the study drug, 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 may jeopardize the patient's safety if he or she continues receiving study drug
- Use of another systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1.

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

4.6.3 Study and Site 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.

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 Conference on 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™) obtained accelerated approval in the USA in May 2016, for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression (1) during or following platinum-containing chemotherapy and/or (2) within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. In October 2016, atezolizumab was approved in the USA for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy. Approval for the same indications was subsequently obtained in Europe. Based on results of the primary analysis of the IMpassion130 (WO29522) study (Schmid et al. 2018), atezolizumab in combination with nab-paclitaxel received accelerated approval by the US FDA in March 2019 for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1. The clinical development of atezolizumab in other advanced or metastatic cancer types is ongoing.

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 Sections 4.1.1 and 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 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 atezolizumab/placebo 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; refer to Section 5.3.1 for further details. Adverse events will be defined and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0). All serious adverse events and protocol defined events of special interest will be reported in an expedited fashion (see Sections 5.2.2 and 5.2.3, respectively).

Guidelines for management of specific adverse events and for atezolizumab/placebo dosing interruption or discontinuation are provided in Sections 5.1.4 and 5.1.5.3.1, respectively. Guidelines for paclitaxel dosage modification and treatment interruption or discontinuation due to toxicity are provided in Section 5.1.4.2.2. 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).

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 4.2.1 for details.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimise 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. The risks associated with atezolizumab include infusion-related reactions (IRRs) and *immune-mediated* hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, hypophysitis, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis; refer to Section 5.2.3. *Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab).* Additional details regarding clinical safety are provided 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.

5.1.3 Risks Associated with Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. Therefore, study patients may be premedicated according to local paclitaxel prescribing information and institutional standard of care practice. Such premedication may consist of a corticosteroid (dexamethasone 8 - 10 mg PO administered approximately 12 and 6 hours before paclitaxel), diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and a H_2 antagonist (cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before paclitaxel). Patients who experience severe hypersensitivity reactions to paclitaxel despite premedication must not be rechallenged with the drug.

Warnings related to paclitaxel use include bone marrow suppression (primarily neutropoenia), which is dose-dependent and is the dose-limiting toxicity during paclitaxel treatment, with neutrophil nadirs occurring at a median of 11 days. Infectious episodes occurred in 30% of all patients exposed to paclitaxel in clinical trials; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropoenia. Thrombocytopenia (platelet count below 100,000 cells/mm^3 at least once while on treatment) was reported in 20% of the patients, with bleeding episodes in 14% of all patients receiving paclitaxel in clinical trials. Anaemia (haemoglobin <11 g/dL) was observed in 78% of all patients and was severe (haemoglobin <8 g/dL) in 16% of the cases, with no consistent relationship between dose or schedule and the frequency of anaemia.

Other warnings for paclitaxel use include severe cardiac conduction abnormalities (documented in <1% of patients), which required pacemaker placement in some cases. In addition, paclitaxel can cause foetal harm when administered to a pregnant woman.

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel (in 12%, 3%, and 1% of patients, respectively), but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Other significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients, and included syncope, rhythm abnormalities, and venous thrombosis.

Paclitaxel treatment is frequently associated with peripheral neuropathy; however, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of the drug. Other serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site; more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have also been reported, with onset during or up to 10 days after paclitaxel infusions.

Caution should be exercised when paclitaxel is concomitantly administered with known substrates, inhibitors, and inducers of CYP3A4 or CYP2C8; refer to Section 4.4.3.

For more details regarding the safety profile of paclitaxel, refer to the local paclitaxel prescribing information.

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

5.1.4 Management of Patients Who Experience 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-mediated* adverse events, including but not limited to, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic, or eye toxicity refer to Appendix 11 of the protocol, and the current atezolizumab Investigator's Brochure.

5.1.4.1 Pulmonary events/Pneumonitis

5.1.4.1.1 Atezolizumab

Management guidelines for pulmonary events are provided in the current atezolizumab Investigator's Brochure and in Appendix 11.

5.1.4.1.2 Paclitaxel

Pneumonia, interstitial pneumonia, pleural effusion, lung fibrosis, pulmonary embolism, and respiratory failure are rare adverse effects, occurring in ≥1/10,000 and <1/1,000 of patients, and dyspnoea is a common adverse effect, occurring in ≥1/100 and <1/10 of patients treated with paclitaxel. Paclitaxel, particularly in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of interstitial or radiation pneumonitis. Fatal cases of pneumonia have also been reported.

Paclitaxel should be permanently discontinued upon ruling out infectious aetiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. After infectious aetiology is ruled out, IV high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary

pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide.

Refer to the local paclitaxel prescribing information for further details.

5.1.4.2 Infusion-Related Reactions

5.1.4.2.1 Atezolizumab

No premedication is indicated for the administration of atezolizumab in Cycle 1. However, patients who experience an infusion-related reaction with atezolizumab in Cycle 1 may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Guidelines for medical management of infusion-related reactions *or cytokine-release syndrome* are provided in Table 15 and Appendix 11.

5.1.4.2.2 Paclitaxel

Paclitaxel infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema, or generalised urticaria; these events should be treated with aggressive symptomatic therapy; refer to Section 5.1.5.2.2.

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 paclitaxel) 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.

When treatment is temporarily interrupted because of toxicity caused by atezolizumab/placebo or paclitaxel, the treatment cycles will be restarted such that the atezolizumab/placebo and paclitaxel infusions remain synchronised.

If it is anticipated that paclitaxel will be delayed by ≥2 weeks, then atezolizumab/placebo should be given without the chemotherapy, as long as there is no contraindication.

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 28 days, and dosing on Days 8 and 15 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.

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;
- Life-threatening *immune-mediated* hyperthyroidism;
- 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 2 ocular event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 ocular event;
- Grade 3 dermatologic event that has not resolved to Grade ≤1 within 12 weeks, or any Grade 4 dermatologic event;
- 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; any Grade 3 or 4 *immune-mediated* neuropathy; myasthenia gravis or Guillain-Barre syndrome (any grade);
- Grade 2 myocarditis that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 myocarditis;
- Grade 2 or 3 hypophysitis that has not resolved to Grade ≤1 within 12 weeks, recurrent or any Grade 4 hypophysitis;
- Grade 2 renal event/nephritis that has not resolved to Grade ≤1 within 12 weeks, or any Grade 3 or 4 renal event/nephritis;
- Grade 2 or 3 *immune-mediated* myositis that has not resolved to Grade ≤1 within 12 weeks, recurrent Grade *3* myositis.

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. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. 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 the extended period of time must be agreed upon by the investigator and the Medical Monitor. For further details, including complete management guidelines for the above listed *immune-mediated* events, refer to the current atezolizumab Investigator's Brochure and Appendix 11.

5.1.5.2.2 Paclitaxel

Paclitaxel infusion should be discontinued immediately in case of severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema, or generalised urticaria; these events should be treated with aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

In addition, paclitaxel should be permanently discontinued upon ruling out infectious aetiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. Consideration may be given to performing pulse oximetry and pulmonary function tests to confirm respiratory and ventilation compromise in patients with suspected pneumonitis.

Other events that required discontinuation of paclitaxel in clinical trials include cases of severe neurotoxicity, such as peripheral neuropathies (1% of all patients). Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.

Refer to the local paclitaxel prescribing information for further details.

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 infusions may be temporarily suspended in case of an adverse event that requires a dose to be held. If atezolizumab/placebo is held because of adverse events for >12 weeks beyond the last dose, then the patient will be discontinued from atezolizumab/placebo treatment and will be followed for safety as specified in Section 5.5. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold of >12 weeks, study drug may be restarted with the approval of the Medical Monitor.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab/placebo may be held for up to 12 weeks until steroids are discontinued or reduced to prednisone dose (or dose equivalent) of ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

5.1.5.3.2 Paclitaxel

Haematologic Toxicities

Absolute neutrophil count (ANC) must be ≥1500/μL (≥1500 cells/mm^3) and platelet count must be ≥100,000/μL (≥100,000 cells/mm^3) for the patient to receive paclitaxel on any treatment day (Day 1, 8, 15 of any 28-day cycle).

Dose modifications should be made according to the following table:

ANC		Platelets	Paclitaxel dose
≥1,500/μL (≥1,500 cells/mm^3)	and	≥100,000/μL (≥100,000 cells/mm^3)	90 mg/m^2
1,000-1,499/μL (1,000-1,499 cells/mm^3)	or	75,000-99,999/μL (75,000-99,999 cells/mm^3)	65 mg/m^2
<1,000/μL (<1,000 cells/mm^3)	or	<75,000/μL (<75,000 cells/mm^3)	Hold [1]

[1] If treatment is held, the CBC should be repeated until ANC ≥1500/μL (≥1500 cells/mm^3) and platelets ≥100,000/μL (≥100,000 cells/mm^3). If paclitaxel therapy must be held for > 3 weeks to allow for resolution of haematologic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving atezolizumab/placebo.

For any patient experiencing any of the following haematologic toxicities, the paclitaxel dose should be reduced to 65 mg/m² for all subsequent cycles:

- Fever (>38.5°C) associated with ANC <1,000/μL (<1,000 cells/mm^3)
- Absolute granulocyte count <500/μL (<500 cells/mm^3) for > 5 days
- Significant bleeding associated with a platelet count <40,000/μL (<40,000 cells/mm^3)
- Any platelet count <20,000/μL (<20,000 cells/mm^3).

If these severe haematologic toxicities recur in subsequent cycles despite dose reduction, paclitaxel should be discontinued, however the patient may continue receiving atezolizumab/placebo.

If the start of a cycle is delayed (i.e. both atezolizumab/placebo and paclitaxel are held) for low counts, Day 1 will be postponed, and dosing resumed when ANC recovers to ≥1500/μl (≥1500 cells/mm^3) and platelet count returns to ≥100,000/μl (≥100,000 cells/mm^3).

In certain situations, (see Section 5.1.5.1) a cycle may begin with the administration of atezolizumab/placebo alone (without paclitaxel on Day 1). If paclitaxel cannot be administered on Day 8 of the cycle, it may be administered on Day 15 if counts have recovered to permissible levels. If paclitaxel cannot be administered on Day 15 of the cycle, the next dose of paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels.

Hepatic Toxicities

In case of hepatic toxicities, dose modifications should be made according to the following table:

AST		Bilirubin	Paclitaxel dose
≤ 5 x ULN	And	≤ 1.5 mg/dL (≤ 25.65 µmol/L)	90 mg/m^2
> 5 but ≤ 10 x ULN	Or	1.6 - 2.5 mg/dL (27.36 - 42.75 µmol/L)	65 mg/m^2
> 10 x ULN	Or	≥ 2.6 mg/dL (≥ 44.46 µmol/L)	Hold [1]

AST: aspartate aminotransferase; ULN: upper limit of normal

[1] Hold therapy until AST < 10 x ULN and bilirubin < 2.5 mg/dL. If paclitaxel must be held for > 3 weeks to allow for resolution of hepatic toxicity, the patient will discontinue paclitaxel treatment but may continue receiving atezolizumab/placebo.

Patients requiring a delay in paclitaxel therapy due to hepatic toxicity should be evaluated for possible progressive hepatic metastases.

Peripheral Neuropathy

If grade 3 toxicity develops, paclitaxel treatment should be withheld until the neuropathy recovers to < grade 1 (atezolizumab/placebo treatment should continue as scheduled), unless the neuropathy is thought to be immune ***mediated*** [refer to Appendix 11, Table 18, Management Guidelines for Neurologic Disorders]). When treatment is resumed, the paclitaxel dose should be reduced permanently to 65 mg/m². If grade 3 neuropathy persists for > 3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel treatment but may continue receiving atezolizumab/placebo.

Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with standard antiemetics and will not result in dose modification.

Anaphylaxis/Hypersensitivity

- Mild symptoms (e.g., mild flushing, rash pruritus): No treatment needed. Supervise at bedside and complete paclitaxel infusion.
- Moderate symptoms (moderate flushing, rash, mild dyspnoea, chest discomfort): Stop paclitaxel infusion. Administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). After recovery of symptoms, resume infusion at half the previous rate for 15 minutes. If no further symptoms occur, complete the infusion at the full dose rate. If symptoms recur, the reaction should be reported as an adverse event and the patient will discontinue paclitaxel treatment but may continue atezolizumab/placebo.
- Severe life-threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilators, generalised urticaria): Stop the infusion and administer diphenhydramine 25 mg (or equivalent) and dexamethasone 10 mg IV (or equivalent). Add epinephrine or bronchodilators if needed. The reaction should be reported as an adverse event and the patient will discontinue paclitaxel treatment but may continue atezolizumab/placebo.

Gastrointestinal Toxicity

If the patient develops any other grade 3 or 4 toxicity considered related to paclitaxel, paclitaxel should be held until symptoms resolve to grade 1 or less (atezolizumab/placebo treatment should continue as scheduled). When treatment is resumed, the paclitaxel dose should be reduced permanently to 65 mg/m². If grade 3 toxicity persists for >3 weeks or recurs after dose reduction, the patient will discontinue paclitaxel treatment but may continue atezolizumab/placebo.

Refer to the local paclitaxel prescribing information for further details.

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 subject administered 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), except as described in Section 5.3.5.9;
- 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 hospitalisation (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 v4.0; 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 include the following conditions which may be suggestive of an autoimmune disorder:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT >10 x ULN
- Systemic lupus erythematosus

- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, *and* systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune haemolytic anaemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis).

The following events also require immediate reporting:

- Cases of potential drug-induced liver injury that include elevated ALT or AST levels in combination with either elevated bilirubin levels 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.

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 atezolizumab/placebo 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 period (defined as 90 days after the last dose of atezolizumab/placebo) 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 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 NCI CTCAE (Version 4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[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] 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 related to the study drug, and answer "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

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, ambiguous terms such as "systemic reaction" should be avoided. If a patient experienced both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF.

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, except for 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 not be repeatedly recorded on the Adverse Event eCRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (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 x ULN) 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 ULN or >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 ULN or >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 occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of mTNBC should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, 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.

The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the 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.

During survival follow-up, deaths attributed to progression of mTNBC should be recorded only on the Survival eCRF, while the date of death should be captured on the Study Discontinuation eCRF. 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 Long-Term Survival Follow-Up eCRF.

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. 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 Hospitalisation or Prolonged Hospitalisation

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

The following hospitalisation scenarios are not considered to be adverse events:

- Hospitalisation for respite care

- Planned hospitalisation required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalisation for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalisation 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
- Hospitalisation due solely to progression of the underlying cancer (including symptoms).

The following hospitalisation scenario is not considered to be a serious adverse event, and should be reported as an adverse event instead:

- Hospitalisation 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

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

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. Any overdose or incorrect administration of paclitaxel should be noted on the Paclitaxel Administration eCRF and reported as a protocol deviation.

All adverse events associated with an overdose or incorrect administration of the study treatment (atezolizumab/placebo or paclitaxel) should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria, 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

PRO measures to be collected in the study are described in Section 4.5.8. The methods for collecting and analysing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, adverse event reports will not be derived from PRO data by the Sponsor, and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator should determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

Safety analyses will not be performed using PRO data. PRO data will be presented in tables, figures, and data listings separate from the adverse event data, and will be included in the appropriate section of the final study report.

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 (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

Medical Monitor Contact Information

Medical Monitor:	[redacted], MD (Primary)
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted], MD (Secondary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, 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 (listed above and/or on the Roche Medical Emergency List), 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 (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. 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.

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 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 electronic data capture (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 to immediately inform the investigator if they become pregnant during the study or within **6 months** after the last dose of study drug. 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 Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of paclitaxel. 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. 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. Once the authorisation has been signed, the investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. 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 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 stabilisation 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, electronic mail, 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

At the treatment discontinuation visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse events of special interest that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of the study drug), if the event is believed to be related to prior treatment with atezolizumab. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient who participated in this study. The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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 Long-Term Survival Follow-Up eCRF.

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
- Summary of Product Characteristics *Accord UK Ltd* for paclitaxel

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, multicentre, randomised, double-blind, two-arm, placebo-controlled study designed to evaluate the efficacy, safety, and PK of atezolizumab plus paclitaxel compared with placebo plus paclitaxel in patients with previously untreated, inoperable locally advanced or metastatic TNBC.

The analysis populations for the Global study are defined as follows:

- ITT population: all randomised patients, whether or not the assigned study treatment was received.
- PD-L1-positive subpopulation: patients in the ITT population whose PD-L1 status is IC 1/2/3 at the time of randomisation.
- PD-L1-negative subpopulation: patients in the ITT population whose PD-L1 status is IC0 at the time of randomisation.
- Response-evaluable population: patients in the ITT population with measurable disease at baseline.
- Duration of response (DoR)-evaluable population: patients in the ITT population with measurable disease at baseline and an objective response.

- Patient reported outcome (PRO)-evaluable population: patients in the ITT population with baseline PRO assessment and at least one post-baseline PRO assessment.
- Safety-evaluable 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.

If additional enrolment in China is initiated, data from this phase will not be included in the primary analysis of global study. A separate analysis will be performed for China population (i.e. patients enrolled from China in both 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

6.1.1 Global Study

The purpose of this event-driven study is to evaluate the efficacy of atezolizumab plus paclitaxel compared to placebo plus paclitaxel as measured by PFS (either investigator-assessed disease progression per RECIST v1.1 or death from any cause, whichever occurs first).

PFS will be assessed hierarchically in the following fixed order: (1) PFS in the PD-L1-positive subpopulation; followed by (2) PFS in the ITT population.

The sample size for the Global study is determined based on the following assumptions:

- Median PFS of 5.0 months in patients with PD-L1-positive tumour status randomised to the placebo plus paclitaxel group (as detected in patients with PD-L1-positive TNBC in the placebo plus albumin-bound (nab-)paclitaxel control arm of the IMpassion130 study) (Schmid et al. 2018);
- Treatment effect (between-group difference) of 2.5 months in the median PFS (HR 0.62) in the PD-L1-positive subpopulation (as detected in the PD-L1-positive subpopulation of the IMpassion130 study) (Schmid et al. 2018);
- Randomisation ratio of 2:1;
- Approximately 40% of the enrolled patients are expected to have PD-L1-positive tumour status (as detected in the IMpassion130 study) (Schmid et al. 2018);

- 80% power and an overall 2-sided α of 0.05;
- Drop-out rate of 10%.

Based on these assumptions and parameters, approximately 213 evaluable patients with PD-L1-positive tumour status (approximately 142 in the atezolizumab plus paclitaxel group and approximately 71 in the placebo plus paclitaxel group) and a total of 155 PFS events are required to detect a between-group difference of 2.5 months in the final analysis of median PFS (HR 0.62). Assuming that approximately 40% of the enrolled patients will have PD-L1-positive tumour status, and to account for an estimated drop-out rate of 10%, approximately 600 patients will be randomised in the Global study (approximately 400 in the atezolizumab plus paclitaxel group and approximately 200 in the placebo plus paclitaxel group). Anticipating a global recruitment period of approximately 23 months (up to 40 patients per month), the clinical cut-off (CCO) date for the primary (final) PFS analysis in the subpopulation with PD-L1-positive tumour status is expected to occur approximately 29 months after the first patient was randomised (FPI) in the Global study.

In addition, overall survival (OS) is a secondary analysis in this study. As for the primary analysis of PFS, OS will be analysed in the PD-L1-positive subpopulation and ITT population. Based on the previously noted assumptions, with an anticipated global recruitment period of approximately 23 months (up to 40 patients per month) and assuming that in the subpopulation with PD-L1-positive tumour status, median OS will be 15.5 months in the placebo plus paclitaxel group (based on the median OS in the PD-L1-positive subpopulation receiving nab-paclitaxel only in the IMpassion130 study (Schmid et al. 2018), the study will have approximately 70% power to detect a between-group difference of 9.5 months in the median OS (HR 0.62). The final analysis of OS should occur after 122 mortality events have been observed in the subpopulation with PD-L1-positive tumour status, which is expected approximately 40 months after FPI. By this time-point, 305 mortality events are expected to have occurred in the ITT population.

Operating characteristics (power and expected total number of events) for HR values for median PFS and median OS in the PD-L1-positive subpopulation are provided in Table 7.

Table 7 Operating Characteristics for the Global Study

	Total	ATZ+PAC	PL+PAC	Treatm. Δ	HR	Power	Duration of Study
mPFS, PD-L1-positive Subpopulation (Primary)	-	7.5 mo	5.0 mo	2.5 mo	0.62	80%	29 mo
Total events	155	-	-				
Evaluable Pts	~213	~142	~71				
mPFS, ITT Population (Primary)	-	-	-	-	-	-	-
Total events	~395						
Evaluable Pts	~540	~360	~180				
Total Pts	~600	~400	~200				
mOS, PD-L1-positive Subpopulation (Secondary)	-	25.0 mo	15.5 mo	9.5 mo	0.62	≈70%	40 mo
Total events	122	-	-	-	-	-	-

ATZ=atezolizumab; HR=hazard ratio; m=median; mo=months; PAC=paclitaxel; PFS=progression-free survival; PL=placebo; OS=overall survival

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed; mPFS in the control arm is 5.0 months, and patients are recruited over approximately 23 months (up to 40 patients per month); 2:1 randomisation; overall two-sided $\alpha = 0.05$.

6.1.2 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:

1. PFS by RECIST v1.1 (PD-L1-positive subpopulation)
2. PFS by RECIST v1.1 (ITT population)
3. OS (PD-L1-positive subpopulation)
4. OS (ITT population)
5. Objective response rate (ORR) by RECIST v1.1 (PD-L1-positive Response-evaluable population).
6. ORR by RECIST v1.1 (Response-evaluable population).

The remaining secondary endpoints (12-month and 18-month OS rates, TTD, PFS rate at 12 months, DoR, CBR, as well as C-ORR and C-DoR [added as per FDA request]) will not be adjusted for multiple testing.

OS will also be analysed (in the PD-L1-positive subpopulation and the ITT population) at the primary (final) analyses of PFS, as well as after 122 deaths are observed in the PD-L1-positive subpopulation.

A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets, 1983). Testing on OS will be conducted hierarchically only if testing on PFS has been rejected.

The information fraction at the time of each analysis will be re-calculated using the actual number of events included in the analysis, and the nominal alpha level re-calculated accordingly.

Table 8 Timing of the PFS and OS Analyses

Analysis	Timing of Analysis	Percent Information	Nominal Two-Sided Alpha Level	Cumulative Two-Sided Alpha Level	Power (%)
PFS Primary Analysis	155 PFS events*	100%	-	0.05	80%
OS Interim Analysis	~83 OS events*	67%	0.012	0.012	-
OS Final Analysis	122 OS events*	100%	0.046	0.05	~70%

* Number of outcome events in the PD-L1-positive subpopulation

6.1.3 China Population

After approximately 600 patients have been randomised in the Global study, global recruitment will be closed. Additional patients may be subsequently enrolled in China only, following the same randomisation procedures and ratio (2:1), for a total of approximately 130 patients from mainland China. Assuming that 40% of patients will have PD-L1 positive tumour status, it is estimated that approximately 52 of the 130 Chinese patients will be PD-L1-positive.

Based on the same assumptions as in the Global population with PD-L1-positive tumour status, the China population analysis is planned to be conducted when approximately 36 PFS events have occurred in China population with PD-L1-postive tumour status. This will provide an approximately 77% probability of maintaining ≥ 50% of PFS risk reduction to be observed from the global primary analysis. The recruitment period in China is expected to be approximately 19 months, and the CCO date for China population analysis is expected to occur approximately 23 months after the first Chinese patient is randomised.

Refer to Section 6.12 and the SAP for further details.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, major protocol violations including major deviations of inclusion/exclusion criteria, and discontinuation from the study will be summarised overall and by treatment arm for all randomised patients. The reasons for study discontinuation will be tabulated.

6.3 SUMMARIES OF TREATMENT ARM COMPARABILITY

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 efficacy variable will be defined as the last available value recorded prior to randomisation. The baseline value of any non-efficacy variable will be defined as the last available value recorded on or prior to the first administration of any study medication.

6.4 EFFICACY ANALYSES

Efficacy analyses will be performed separately for the PD-L1-positive subpopulation and the ITT population.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study, 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.

PFS will be assessed hierarchically in the following fixed order:

(1) PFS in the PD-L1-positive subpopulation (defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomisation), followed by

(2) PFS in the ITT population,

with patients grouped according to their treatment assigned at randomisation.

PFS will be compared between treatment arms based on the stratified log-rank test. The stratification factors will be three of the four predefined randomisation stratification factors: tumour PD-L1 status (IC0 vs. IC1/2/3), prior taxane treatment (yes vs. no) and presence of liver metastases (yes vs. no) and will be obtained from the interactive Web/phone response system (IxRS). The hazard ratio (HR) for disease progression or death will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

Data for patients without disease progression or death will be censored at the last tumour assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumour assessment prior to the missed visits as a sensitivity analysis. If no tumour assessment was performed after randomisation, data will be censored at the date of randomisation +1 day.

The CCO date for the primary (final) analysis of PFS will take place when the required number of 155 PFS events have been observed in the PD-L1-positive population. This is projected to occur approximately 29 months after FPI.

Further details will be included in the SAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- OS, assessed in the:
    - PD-L1-positive subpopulation;
    - ITT population;
- ORR, by investigator assessment using RECIST v1.1 (see Appendix 3), assessed in the:
    - PD-L1-positive Response-evaluable subpopulation;
    - ITT Response-evaluable population;
- 12-month and 18-month OS rates in the ITT population;
- Time to deterioration (TTD) in Global Health Status/HRQoL (items 29 and 30 of the EORTC QLQ-C30), in the PRO-evaluable population;

- PFS rate at 12 months in the ITT 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 Response-evaluable population.

In addition, as per FDA request, C-ORR and C-DoR will be analysed. Further details will be provided in the SAP.

6.4.2.1 Secondary Endpoint: Overall Survival

Overall survival (OS), defined as the time from randomisation to death from any cause, is a secondary endpoint for the study. OS will be assessed hierarchically in the PD-L1-positive subpopulation and in the ITT population, in a similar manner as PFS.

An interim analysis of OS will be performed at the time of the primary (final) analysis of PFS. The final analysis of OS will take place when the required number of 122 mortality events have been observed in the PD-L1-positive subpopulation. This is projected to occur approximately 40 months after FPI. By this time-point, 305 mortality events are expected to have occurred in the ITT population. A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate for the OS analyses (Lan and DeMets, 1983).

In addition, the 12-month and 18-month OS rates will be compared between the treatment arms.

Further details will be specified in the SAP.

6.4.2.2 Time to deterioration in Global Health Status

Time to deterioration (TTD) in Global Health Status/HRQoL will be analysed based on the PRO-evaluable population. Deterioration in Global Health Status/HRQoL is defined as a minimally important decrease of ≥ 10 points on the Global Health Status /HRQoL scale (items 29 and 30) of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

Refer to Section 6.7 for a detailed description of the PRO endpoints and corresponding analyses.

6.4.2.3 Secondary Analyses of Progression-Free Survival

PFS rate at 12 months: all patients alive with known progression status at 12 months post-randomisation will be included in the analysis, and the percentages of survivors without a progression event along with the corresponding 95% confidence intervals will be reported by treatment arm.

Further details will be provided in the SAP.

6.4.2.4 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 (ORR) is defined as the proportion of patients who have an objective response. ORR will be analysed using 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.

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 PFS. 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 during the conduct of the study. Confirmed ORR will be derived as per details provided in the SAP.

6.4.2.5 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 PD 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 during the conduct of the study. Confirmed DoR will be derived as per details provided in the SAP.

6.4.2.6 Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the percentage of patients who have achieved either unconfirmed CR, or unconfirmed PR, or stable disease (SD) that lasts at least 6 months. CBR will be displayed by treatment arm.

6.4.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be analysed by cycle, and between the treatment arms using descriptive statistics:

- Second-line PFS (PFS2): PFS2 is defined as time from randomisation to tumour progression or death from any cause on next line of treatment, whichever occurs first. Patients who are alive and who have not experienced disease progression on next

line of treatment at the time of CCO date will be censored at the last date known to be alive. PFS2 will be compared between treatment arms in the subset of patients receiving second-line treatment using similar method as the primary endpoint of PFS; refer to Section 6.4.1;

- Changes from baseline score in patient function (physical, role, social, emotional, cognitive) and disease/treatment-related symptoms, as assessed by all function scales and symptom items/scales of the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23);
- Changes from baseline score in overall health and quality of life, as assessed by the Global Health Status/HRQoL scale (items 29 and 30) of the EORTC QLQ-C30;
- Health Economic data: Health utility scores derived from the EQ-5D-5L and EQ-VAS questionnaires;
- Burden of treatment: Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G.

Further details on the analysis of exploratory PRO endpoints are provided in Section 6.7.2 and in the SAP.

6.4.4 Handling of Missing Data

For PFS analyses, patients without a date of disease progression will be analysed as censored observations at the last tumour assessment date. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the date of the PFS event will be censored at the last tumour assessment prior to the missed visits as a sensitivity analysis. If no post-baseline tumour assessment is available, data will be censored at the date of randomisation +1 day (see Section 6.4.1).

For OS, patients who are not reported as having died will be analysed as censored observations 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 objective response, patients without any post-baseline assessment will be considered non-responders.

Handling of missing PRO data is described in Section 6.7.

6.5 SAFETY ANALYSES

Safety analyses will include all randomised patients who received at least one dose of study treatment (atezolizumab/placebo or paclitaxel), 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 (defined as events occurring on or after the first dose of study treatment and within 30 days prior to the last dose of study treatment) 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 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 by time, 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 6.8.

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.

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.

Plasma concentrations of paclitaxel (reported as total paclitaxel) will be measured at specific timepoints (see Appendix 2), tabulated and summarised. The concentration data will be summarised with use of descriptive statistics as stated above.

Additional PK analyses will be conducted as appropriate.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

Analyses of PRO measures will be completed on the PRO-evaluable population, defined as patients in the ITT population with baseline PRO assessment.

6.7.1 Analysis of Time to Deterioration in Global Heath Status

The primary patient-reported endpoint is the TTD in Global Health Status/HRQoL. Deterioration in Global Health Status/HRQoL (Items 29, 30 of the EORTC QLQ C30) is

defined as 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). Data for patients who do not achieve a 10-point decrease will be censored at the last time PRO data are available. Only patients with baseline global health status/HRQoL scores will be included in the analysis. Data for patients without at least one post-baseline assessment will be censored at the date of randomisation + 1 day.

TTD in global health status/HRQoL will be compared between the treatment arms using the same method as the primary endpoint of PFS.

6.7.2 Exploratory Patient-Reported Outcomes Analyses

6.7.2.1 Changes from Baseline in Patient Function and Symptoms (EORTC QLQ C30 and QLQ BR23)

Changes from baseline in patient function (physical, role, social, emotional, cognitive) and disease/treatment-related symptoms, using the EORTC QLQ-C30 questionnaire and its breast cancer module (QLQ-BR23), will also be assessed.

Summary statistics (mean, standard deviation, median, and range) of absolute scores and mean changes from baseline will be calculated for all items and subscales of the EORTC QLQ-C30 and QLQ-BR23 at each assessment timepoint for each treatment arm while on treatment. The mean (and 95% CI) and median of the absolute scores and the changes from baseline will be reported for interval and continuous variables. Previously published MIDs will be used to identify meaningful change from baseline within each treatment arm on the functional and disease/treatment-related symptoms scales (Osoba et al. 1998; Cocks et al. 2011).

A time-to-event analysis to investigate the time to clinically meaningful deterioration in the functional (physical, role, and cognitive) subscales of the EORTC QLQ-C30 will be conducted to assess the time from baseline to worsening in patient function. Deterioration in function will be assessed using the published corresponding MIDs (Cocks et al. 2011). Only patients with baseline scores will be included in the analysis. Patients who do not achieve an MID based on published thresholds will be censored at the last time PRO data are available. Patients without at least one post-baseline assessment will be censored at the date of randomisation +1 day. A stratified log-rank test will be used to test the differences between treatment arms.

A longitudinal analysis will be conducted to estimate the effect difference on PRO repeated responses over a selected time-period 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% confidence intervals 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 2001). 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 published validation reports. 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.

6.7.2.2 Changes from Baseline in Overall Health and Quality of Life (EORTC QLQ C30, Items 29 and 30)

Changes from baseline score for overall health and quality of life (items 29 and 30, respectively of the EORTC QLQ-C30) will be evaluated for patients with a baseline and at least one post-baseline assessment. For both items, scores will be derived from a seven-point scale (from 1 = very poor to 7 = excellent). Summary statistics (mean, standard deviation, median, and range) of absolute scores and mean changes from baseline will be calculated for both items at each assessment timepoint for both treatment arms while on treatment, as described in Section 6.7.2.1.

6.7.2.3 Health Economic 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 (CSR).

6.7.2.4 Burden of Treatment

In this study, the burden of treatment associated with the addition of atezolizumab to paclitaxel will be measured by the GP5 item ("I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G quality of life instrument (Cella et al. 1993). GP5 item scores will be derived from a five-point scale from 0 (not at all) to 4 (very much). Item GP5 from version 4 of the FACT-G questionnaire will be scored according to the FACIT scoring manual (Cella 1997). A descriptive analysis of absolute scores and the proportion of patients selecting each response option at each assessment timepoint 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 (see Appendix 4).

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one pre-dose and one post-dose ADA assessment, with patients grouped according to treatment received.

Patients will be classified as ADA positive if they were ADA negative at baseline 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 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 during both the treatment and follow-up periods will be summarised by treatment arm and listed by patient and cycle.

Exploratory immunogenicity endpoints will be analysed and reported descriptively.

6.9 BIOMARKER ANALYSES

To evaluate the dependency of the action of the drug combination (atezolizumab plus paclitaxel) according to prospectively determined PD-L1 expression, analyses of the relationship between PD-L1 status by immunohistochemistry (PD-L1-negative: IC0 vs PD-L1-positive: IC 1/2/3) in tumour tissues obtained prior to randomisation, and clinical efficacy and safety outcomes will be undertaken.

6.9.1 Exploratory Biomarker Analyses

Exploratory biomarker analyses (in tumour tissues, plasma, and whole blood) will be performed to evaluate the association of these markers with study drug response, including efficacy and/or adverse events.

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 (obtained at baseline/prior to randomisation, on-treatment, and at disease progression) and blood and their association with disease status and/or response to study drug, the following will be analysed:

- 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 by NGS genotyping in tumour tissues.
- 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 paclitaxel +/- atezolizumab treatment.
- In addition, correlation of immune biomarker findings in blood and tissue samples from this study to findings from other studies in TNBC and other tumour types will be evaluated.

Results of biomarker analyses will be presented in a separate report.

6.10 SUBGROUP ANALYSES

To assess the consistency of treatment benefit study results in subgroups defined by demographic and relevant baseline characteristics (including geographical region), PFS and OS in these subgroups will be evaluated.

Consistency of treatment benefit across geographical regions and other relevant demographic and baseline characteristics will be assessed using stratified Cox Proportional hazards models, and hazard ratios with 95% confidence intervals will be estimated. Forest plots will be used to summarise the results. As indicated by the data, random effects models might be used to further explore potential region/centre effects. Further details will be specified in the SAP.

6.11 INTERIM ANALYSIS

The iDMC will review safety data periodically during the study. All summaries/analyses by treatment arm for iDMC review will be prepared by an iDCC. See Section 3.1.2 for additional details regarding the iDMC.

6.11.1 Planned Interim Analysis

There will be one interim analysis of OS (in the PD-L1-positive subpopulation and the ITT population) at the primary (final) analysis of PFS. The final analysis of OS will be performed after 122 deaths are observed in the PD-L1-positive subpopulation.

A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets, 1983). Testing on OS will be conducted hierarchically only if the null hypothesis for testing on PFS has been rejected.

The information fraction at the time of each analysis will be re-calculated using the actual number of events included in the analysis, and the nominal alpha level re-calculated accordingly.

6.11.2 Optional Interim Analysis

To adapt to information that may emerge during the study, the Sponsor may also choose to conduct an interim efficacy analysis, based on a recommendation from the iDMC and in consultation with the Steering Committee. If such an interim analysis is conducted, 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 2 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, and the iDMC charter will also be made available to relevant health authorities.

6.12 CHINA POPULATION ANALYSES

The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel 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).

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.

Analysis of the efficacy endpoints will be performed for the China population in a similar way as done for the Global population described in Section 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 and PK data for the China population will be analysed using the same methods as described in Sections 6.5 and 6.6, respectively.

The results of the China population analyses will be summarised in a separate CSR.

Further details will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for 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 Sponsor.

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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an electronic device to capture PRO data. The data will be transmitted via web automatically after entry to a centralised database maintained by the Sponsor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 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 7.6.

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.

7.5 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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 USA 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 Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent

Form, if applicable) 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 Informed Consent Forms 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 Informed Consent Form 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.

Patients participating in the study must be re-consented to the most current version of the Consent Forms, or to a significant new information/findings addendum, according to the applicable local law and IRB/EC policy. 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 USA, each Consent Form may also include patient authorisation 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 utilises a separate Authorization Form for patient authorisation 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 Informed Consent Forms, 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 Informed Consent Form (or separate authorisation 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.

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 (i.e., LPLV).

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, Informed Consent Forms, 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.

9.3 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.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann La Roche Ltd.

Approximately 600 patients will be randomised at approximately 200 sites globally (in select countries from Europe, Asia/Pacific, as well as North-, and South America) over approximately 23 months. This total accounts for an estimated 10% drop-out rate during the study. Patients will be randomised centrally, using an IxRS (ALMAC Clinical Technologies).

Total recruitment in China (to randomise approximately 130 patients in the Global study and during additional enrolment in China combined) will be approximately 19 months.

Clinical operations, data management, day-to-day clinical science monitoring, and statistical programming responsibilities will be outsourced. The global CRO will be Chiltern International.

Central testing laboratories will be responsible for the following:

- Prospective testing of PD-L1 and retrospective confirmation of ER, PR, and HER2 triple negative status

- Biomarker assays (blood-based and tumour sample-based)
- PK assays
- ADA assays
- Auto-antibody testing
- CRP testing.

Supply kits for all central laboratory assessments will be provided by Covance Inc. Biomarker analyses, including PD-L1, ER, PR, and HER2 testing will be completed by HistoGeneX.

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 Steering Committee (SC) and the independent Data Monitoring Committee (iDMC) will be provided in the SC Charter and iDMC Charter, respectively.

9.5 PUBLICATION 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 and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

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 authorisation 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 CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorisation 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.

9.6 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).

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Appendix 1
Schedule of Activities

Assessment Day (Window)	Screening	Baseline	All Cycles [a1]			Treatment Discontinuation [b]	Follow-Up Every 3 months (± 21 days)
	Days -28 to -1	Days -7 to -1	Day 1 [a2]	Day 8 (± 3) [a3]	Day 15 (± 3)	30 (± 5) Days after Last Dose	
Signed Informed Consent Form(s) [c]	x						
Review of eligibility criteria	x	x					
Demographics [d]	x						
Medical, surgical, and cancer histories [d]	x						
Head CT or MRI	x						
HIV, HBV, HCV serology [e]	x						
Concomitant medications [f]	x	x	x	x	x	x	
Tumour assessment [g]	x		See footnote [g]			x	x [g]
EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L [h1]			x			x	x [h1]
FACT-G, Single Item GP5 [h1, h2]			x [h2]			x	x [h1]
Physical examination [i]	x	(x) [i]	x [i]			x	
ECOG performance status	x	(x) [j]	x [j]			x	
Vital signs [k]	x		x	x	x	x	
12-lead electrocardiogram [l]	x		Perform as clinically indicated				
Weight	x		x			x	
Height	x						
Haematology and Serum chemistry [m]	x	(x) [j]	x [j]	x	x	x	
Coagulation panel (aPTT, INR)	x					x	
C-reactive protein testing	x	(x)	x				
Urinalysis [n]	x						

Appendix 1
Schedule of Activities (cont.)

Assessment Day (Window)	Screening	Baseline	All Cycles [a1]			Treatment Discontinuation [b]	Follow-Up Every 3 months (± 21 days)
	Days -28 to -1	Days -7 to -1	Day 1 [a2]	Day 8 (± 3) [a3]	Day 15 (± 3)	30 (± 5) Days after Last Dose	
Pregnancy test (WOCP only)		x [o]	x [p]			x [p]	
TSH, free or total T3, free T4 [q]	x		x [q]			x	
Auto-antibody testing [r]			x				
Serum sample for ADA assessment [s]			x			x	
Serum sample for atezolizumab PK evaluations [s]			x			x	
Plasma samples for paclitaxel PK evaluations [s]			x			x	
Whole blood for exploratory biomarker analysis [s]			x [s]			x	
Plasma for exploratory biomarker analysis [s]			x [s]			x	
Whole blood sample for germline DNA analysis [t]		x					
Randomisation			x				
Adverse events [u]			x	x	x	x	
Atezolizumab/placebo infusion [v]			x		x		
Paclitaxel administration [a3]			x	x	x		
Mandatory FFPE tumour tissue sample [w]	x [w]						
Optional FFPE tumour tissue samples [x,y]			Only at Cycle 2 Day 1 [x]			x [y]	
Survival and anti-cancer therapy follow-up [z]							x

Appendix 1
Schedule of Activities (cont.)

ADA = anti-drug antibody; CT = computerized tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; ePRO = electronic patient-reported outcome; EQ-5D-5L = European Quality of Life 5 Dimensions, 5 level; FFPE = formalin fixed paraffin embedded; HBcAb = antibody to hepatitis B core antigen; HBsAb = antibody to hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PDL1 = programmed death ligand 1; PK = pharmacokinetic; q8w = every 8 weeks; QLQBR23 = Quality-of-life Questionnaire Breast Cancer Module; QLQC30 = Quality-of-life Questionnaire Core 30; PD=disease progression; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone; v = version; WOCP = women of child-bearing potential

[a1] If a scheduled treatment visit cannot be completed due to a holiday, dosing may be postponed to the earliest next date; subsequent dosing should continue according to the original schedule. However, paclitaxel should not be administered more frequently than every 7 days. After five cycles, one of three cycles may be delayed by one week to allow for vacations.

[a2] Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted. An assessment day window of ±3 days for Day1 of cycle ≥2 will be permitted in the study.

[a3] Paclitaxel will be administered at the 90 mg/m^2 dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. Paclitaxel should not be administered more frequently than every 7 days. The Day 8 visits are not required for patients who have discontinued paclitaxel and are continuing treatment with atezolizumab/placebo only.

[b] Patients will be asked to return to the clinic within 30 days after their last study drug dose for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., due to PD) may be used as the treatment discontinuation visit.

[c] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. 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 randomisation (except where otherwise specified) may be used for screening assessments rather than repeating such tests. 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.

[d] Demographic information includes age, gender, and self-reported race/ethnicity. Reproductive status and smoking history should also be captured. Cancer history includes stage, date of diagnosis, and prior anti-tumour treatment.

[e] All patients will be tested for HIV antibody, HBsAg, HBcAb, HBsAb, and hepatitis C virus antibody (HCVAb) locally, prior to the inclusion into the study. HIV-positive patients will be excluded from the clinical trial. In patients with a negative HBsAg and positive HBcAb serology, HBV DNA must also be collected prior to randomisation. Patients positive for HCVAb require a negative PCR for HCV RNA to confirm eligibility.

[f] Includes all prescription or over-the-counter medications taken from 7 days prior to screening to EOS.

[g] 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. Radiologic imaging performed during the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan, 3) CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis, and 4) any other imaging studies (CT neck, plain films, etc.) as clinically indicated/determined by the treating physician. 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. For each patient, the same radiographic procedures and technique must be used throughout the study, and results must be reviewed by the investigator before dosing at the next cycle. Tumour

response will be evaluated using RECIST v1.1 (Appendix 3). During the post-treatment Follow-up period, only patients with no PD will undergo tumour assessments. For patients who discontinue study treatment before EOS for reasons other than PD, tumour assessments will continue until PD, death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor.

[h1] The EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L questionnaires and item GP5 of the FACT-G questionnaire will be completed by the patient on an electronic (ePRO) device either at their home or at the site at baseline (Cycle 1, Day 1, with the exception of item GP5 of the FACT-G; see comment [h2]), on Day 1 of each subsequent cycle, and at the treatment discontinuation visit. In addition, all patients will be asked to complete the PRO questionnaires every 3 months for 1 year after treatment discontinuation, regardless of whether the patient is receiving subsequent anti-cancer therapy. At each visit, PRO questionnaires should be completed before discussion of the patient's health state, lab results, or health record, before administration of study treatment and/or prior to any other study assessments that could bias patients' responses to ensure that the validity of the instrument is not compromised, and that data quality meets regulatory requirements. 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 the ePRO device to and ensure measures have been completed and saved before the patient leaves the investigational site.

[h2] Since item GP5 specifically assesses patients being bothered by the side-effects of treatment, this item will not be administered to patients at baseline (Cycle 1, Day 1). While on study treatment, all patients will complete the FACT-G, single item GP5 beginning on Cycle 2, Day 1 and at Day 1 of every cycle thereafter.

[i] Complete physical examination at Screening, and EOT, and symptom-driven physical examinations within 96 hours before Day 1 of each cycle, 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.

[j] ECOG performance status and local laboratory assessments may be obtained within 96 hours before Day 1 of each cycle.

[k] 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. At all clinic visits where study treatment is administered, vital signs should be determined within 60 minutes before the first infusion. Vital signs will also be determined during and after the infusions if clinically indicated.

[l] 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.

[m] Haematology consists of RBC count, haemoglobin, haematocrit, WBC count with differential (if clinically indicated), and platelet count. Serum chemistry includes BUN, creatinine, sodium, potassium, chloride, bicarbonate, calcium, glucose, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Bicarbonates should only be tested at sites where this test is part of the standard safety laboratory panel. Magnesium and phosphorus should be collected at screening, and thereafter only if clinically indicated. Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms suggestive of pancreatitis.

[n] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood) will be performed at screening, and thereafter only if clinically indicated.

Appendix 1
Schedule of Activities (cont.)

[o] Serum pregnancy test within 7 days before Cycle 1, Day 1.

[p] Urine pregnancy test; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed within 96 hours before Day 1 of Cycle 1, within 96 hours before Day 1 of every second cycle thereafter, and at treatment discontinuation.

[r] Includes antinuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. Baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study treatment. For patients who show evidence of immune mediated toxicity, additional samples will be collected. All samples will be analysed centrally.

[s] See Appendix 2 for a detailed schedule.

[t] 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.

[u] 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.

[v] Patients should receive their first dose of study drug on the day of randomisation (no later than 3 days after randomisation). The first dose of atezolizumab/placebo will be delivered over 60 ± 15 minutes; if well tolerated, all subsequent infusions may be delivered over 30 ± 10 minutes.

[w] Mandatory tumour tissue biopsy collected within 3 months prior to study enrolment. If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent sample should be used. Samples may be collected by core needle or excisional/punch biopsy per investigator discretion. Tumour tissue should be of good quality based on total and viable tumour content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, more than one core (if clinically feasible) should be submitted for evaluation. Retrieval of already available tumour sample can occur outside the 28-day screening period.

[x] Optional on-treatment tumour tissue sample collected before the Cycle 2, Day 1 dose (or within 14 days before the Cycle 2, Day 1 dose) from patients who have provided consent for optional biopsies. Samples may be collected by core needle or excisional/punch biopsy per investigator discretion.

[y] Optional sample, collected (if clinically feasible) at the time (or within ±7 days) of radiographic progression (per RECIST v1.1), preferably from growing lesions.

[z] 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 approximately every 3 months ± 21 days. 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. Information regarding PFS2 and PROs will also be collected during the survival follow-up period.

Appendix 2
Anti-Drug Antibody, Pharmacokinetic, Pharmacodynamic, and Exploratory Biomarker Sampling Schedule

Study Visit	Timepoint	Sample
Screening	Days -28 to -1	Mandatory FFPE tumour tissue sample [c]
Cycle 1, Day 1	Prior to first dose of any study treatment	Atezolizumab PK and ADA [a]
		Plasma sample for biomarker analysis
		Whole blood sample for germline DNA analysis [d]
		Whole blood sample for exploratory biomarker analysis [f]
	30±10 minutes after end of atezolizumab infusion	Atezolizumab PK [a]
	5-10 minutes before the end of paclitaxel infusion	Paclitaxel PK [b]
	1 hour after the end of paclitaxel infusion	Paclitaxel PK [b]
Cycle 2, Day 1	Prior to first dose of any study treatment	Atezolizumab PK and ADA [a]
		Optional FFPE tumour tissue sample [e]
		Plasma sample for biomarker analysis
		Whole blood sample for exploratory biomarker analysis [f]
Cycle 3, Day 1	Prior to first dose of any study treatment	Atezolizumab PK and ADA [a]
		Plasma sample for biomarker analysis
	5-10 minutes before the end of paclitaxel infusion	Paclitaxel PK [b]
	1 hour after the end of paclitaxel infusion	Paclitaxel PK [b]
Cycle 4, Day 1	Prior to first dose of any study treatment	Atezolizumab PK and ADA [a]

Appendix 2
Anti-Drug Antibody, Pharmacokinetic, Pharmacodynamic, and Exploratory Biomarker Sampling Schedule (cont.)

Study Visit	Timepoint	Sample
Cycles 6, 9 and every three cycles thereafter, Day 1	Prior to first dose of any study treatment	Plasma sample for biomarker analysis
At the time of radiographic progression	NA	Optional FFPE tumour tissue sample [e]
		Plasma sample for biomarker analysis
		Whole blood sample for exploratory biomarker analysis [f]
Treatment discontinuation visit	At visit	Atezolizumab PK and ADA [a]

ADA=anti-drug antibody; PD=pharmacodynamic; PK=pharmacokinetics

[a] Samples for atezolizumab PK and ADA will be collected from patients enrolled in the Global Study during the first four cycles of atezolizumab/placebo and at the Treatment discontinuation visit. For patients who discontinue atezolizumab/placebo and continue on paclitaxel alone, the scheduled collection for atezolizumab PK at the treatment discontinuation visit is still required. Patients enrolled in mainland China will not undergo atezolizumab PK and ADA assessments.

[b] Samples for paclitaxel PK were collected from the first approximately 60 patients randomised in the Global Study (Arm A and Arm B). No further sampling for paclitaxel PK will occur in the study. Patients enrolled in mainland China will not undergo paclitaxel PK assessments.

[c] Results of PD-L1 testing of this mandatory baseline tumour sample must be obtained from the designated central laboratory prior to enrolment. The screening sample must have been collected ≤ 3 months from randomisation. If a tumour sample taken within 3 months before randomisation 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. Of these additional options, the most recent sample should be used.

[d] 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.

[e] 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.

[f] Whole blood samples collected at Day 1 of Cycle 1, Day 1 of Cycle 2 and at disease progression are to assess peripheral blood mononuclear cells (PBMCs). Whole blood samples for PBMC analysis have been collected from over 300 patients at baseline; for these patients, sample collection will continue as described in the above table (on C2D1 and at PD). However, for newly enrolled patients, there will be no whole blood sampling for PBMC analysis at any time-point. Patients enrolled in China will not undergo this biomarker assessment.

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]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor 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 of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm 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 no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Nontarget Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), 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.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

[1] For 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or 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.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of 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.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during 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).

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 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, <u>if not, the patient should be considered not evaluable from that point forward.</u> 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.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

<u>TUMOR RESPONSE EVALUATION</u>

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

BASELINE DOCUMENTATION 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 in instances where 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 (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and 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 ≥ 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. Nodal 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 ≥ 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.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

In addition, it is possible to record multiple nontarget 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").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

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 nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) 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 the CT scan that the radiologist may not feel comfortable assigning

an exact measure 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 below measurable limit (BML) 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 BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. 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 maximal longest diameter for the coalesced lesion.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. 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 protocol.

- **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

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall

level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, 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 nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. 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 nontarget 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 or may be described in protocols as "sufficient to require a change in therapy." 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table A provides a summary of the overall response status calculation at each 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 Timepoint Response: 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table B Timepoint Response: 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 only a subset of lesion measurements are made at an assessment, 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more nontarget lesions are not assessed, the response for nontarget lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the nontarget response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table C Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

"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, Table B, and Table C.

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.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or nontarget lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or nontarget lesion.

Appendix 4
Patient-Reported Outcome Instruments

ENGLISH

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):

		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

Appendix 4
Patient-Reported Outcome Instruments (cont.)

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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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 <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4
Patient-Reported Outcome Instruments (cont.)

ENGLISH

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

ENGLISH

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

Appendix 4
Patient-Reported Outcome Instruments (cont.)

Health Questionnaire

English version for the UK

Appendix 4
Patient-Reported Outcome Instruments (cont.)

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 ❑

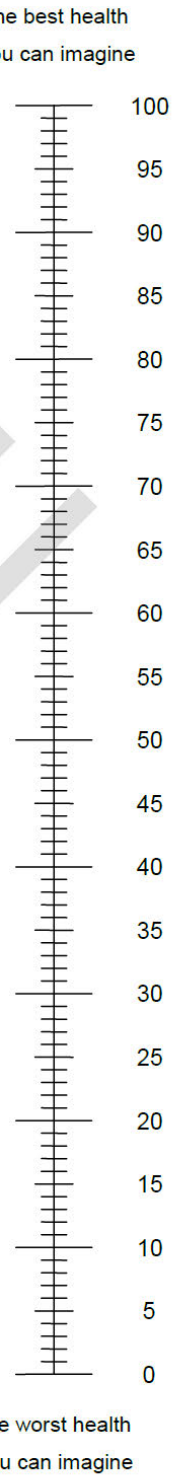
ANXIETY / DEPRESSION

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 ❑

Appendix 4
Patient-Reported Outcome Instruments (cont.)

- 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 = ☐



Appendix 4
Patient-Reported Outcome Instruments (cont.)

FACT-G (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.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

Notes:

Only item GP5 of the Physical Well-being domain of the FACT-4 instrument will be used in the current study.

The remaining three domains of the FACT-G are not shown above.

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). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dysautonomia	Ord's thyroiditis
Addison's disease	Epidermolysis bullosa acquisita	Pemphigus
Ankylosing spondylitis	Gestational pemphigoid	Pernicious anaemia
Antiphospholipid antibody syndrome	Giant cell arteritis	Polyarteritis nodosa
Aplastic anaemia	Goodpasture's syndrome	Polyarthritis
Autoimmune haemolytic anaemia	Graves' disease	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Guillain-Barré syndrome	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	Hashimoto's disease	Psoriasis
Autoimmune hypophysitis	IgA nephropathy	Reiter's syndrome
Autoimmune myocarditis	Inflammatory bowel disease	Rheumatoid arthritis
Autoimmune oophoritis	Interstitial cystitis	Sarcoidosis
Autoimmune orchitis	Kawasaki's disease	Scleroderma
Autoimmune thrombocytopenic purpura	Lambert-Eaton myasthenia syndrome	Sjögren's syndrome
Behcet's disease	Lupus erythematosus	Stiff-Person syndrome
Bullous pemphigoid	Lyme disease - chronic	Takayasu's arteritis
Chronic inflammatory demyelinating polyneuropathy	Meniere's syndrome	Ulcerative colitis
Churg-Strauss syndrome	Mooren's ulcer	Vitiligo
Crohn's disease	Morphea	Vogt-Kovanagi-Harada disease
Dermatomyositis	Multiple sclerosis	Wegener's granulomatosis
	Myasthenia gravis	
	Neuromyotonia	
	Opsoclonus myoclonus syndrome	
	Optic neuritis	

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:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular, subcutaneous, intravenous, and/or endotracheal administration 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 drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
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 as 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 predisease 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 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:

C_{Cr} (creatinine clearance): mL/minute

age: years

Weight: kg

S_{Cr} (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 drug.

- Time course. Exposure to suspect drug. Has the subject 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 recognised 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
Patient Engagement Application

The Patient Engagement Application, a smartphone app, referred to as an “app” that can be used by a subject or the legally authorised representative of a subject in the **MO39196** study.

The App is an optional service that subjects can opt-in to use to remind them of activities/tasks relevant to study compliances like when to take their study medication, attend site visit, track goals. The App also provides supportive guides to help subjects be aware of visit procedures, study information and instructions.

The App’s interactive features are intended to be a companion to the user during the course of a trial and include the following modules:

- Study Information: targeted study information throughout the duration of the study
- Visit Schedule: site visit reminder based on the predefined Schedule of Assessments and treatment groups
- Medications: drug information, dosage, instructions and reminders
- Goals: ability to track personal goals (e.g. weight, exercise, sleep, etc.)
- Reminders: reminders for activities/tasks relevant to study compliances
- Site Information: module where patients can enter their site contacts details

The App is available for download to smartphone devices that support iOS and Android. The app will contain study-specific information only once activated by a subject. The study coordinator will provide the subject with a secure activation code, which they can use to activate the app upon their first use.

The App does not collect any subject identified information or clinical data. This app is intended for informational purposes only. It is not a substitute for professional medical advice. Subjects should contact the study site investigator or coordinator with any medical questions or concerns.

Appendix 11
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 *atezolizumab* 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.

The investigator should consider the benefit–risk balance *for* a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PULMONARY EVENTS

Dyspnoea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumour assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 9.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 9 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.
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. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 10.

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 10 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 10 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish aetiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhoea or colitis are provided in Table 11.

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.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 11 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. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact 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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event 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 Medical Monitor. [c]

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 11 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhoea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 12.

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.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 12 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening *immune-mediated* hyperthyroidism. [c]

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 12 Management Guidelines for Endocrine Events (cont.)

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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event 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 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. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 12 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 13.

Table 13 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 Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. *Immune-mediated* myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, *laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities,* dyspnoea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Immune-mediated* myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of 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 14.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 14 Management Guidelines for *Immune-Mediated* Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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*,* anti-pyretics*, 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 medical management of IRRs *and CRS* are provided in Table 15.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 15 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, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 15 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Grade 2 [a] *Fever [b] with hypotension not requiring vasopressors* *and/or* *Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by*	• I*mmediately i*nterrupt 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. [e]* • *Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.* • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.* • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs *and/or CRS*. • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 15 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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 Medical Monitor. [f] • *Administer symptomatic treatment. [c]* • *For hypotension, administer IV fluid bolus and vasopressor as needed.* • *Monitor cardiopulmonary and other organ function closely; monitoring in the 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. [e]* • *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 Medical Monitor. [f]* • *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. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 15 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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 NCCN guidelines for 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 ℃ 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, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.*

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

[e] *There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.*

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. *For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.*

[g] *Refer to Riegler et al. (2019) for information on experimental treatments for CRS.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 16.

Table 16 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 16 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

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

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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-*limiting*, with or without pruritus. 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 17.

Table 17 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. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterisation to differentiate between alternative aetiologies. Management guidelines for neurologic disorders are provided in Table 18.

Table 18 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate aetiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate aetiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 19.

Table 19 Management Guidelines for *Immune-Mediated* Meningoencephalitis

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED NEPHRITIS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function*. Renal* function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common aetiologies (including prerenal and postrenal causes, and concomitant medications such

as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. 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 20 below.

Table 20 Management Guidelines for *Immune-Mediated* Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, 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 Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact 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 and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. 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 signs and symptoms of myositis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 21 below.

Table 21 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 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 Medical Monitor. [c]

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 21 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact 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 Medical Monitor. [c] • For recurrent events, ***permanently discontinue atezolizumab and contact Medical Monitor***. [c]

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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), which are considered to be potential risks for atezolizumab.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). 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 ×10⁹/L (100,000/μL)*
  - *ANC <1.0 ×10⁹/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 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms*

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). 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 ×10⁹/L (181,000/μL)*
  - *AST ≥48 U/L*
  - *Triglycerides >1.761 mmol/L (156 mg/dL)*
  - *Fibrinogen ≤3.6 g/L (360 mg/dL)*

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 22.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 22 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	*Management*
Suspected HLH or MAS	• *Permanently discontinue atezolizumab and contact 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 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.*

HLH =hemophagocytic lymphohistiocytosis; MAS =macrophage activation syndrome.

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