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

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS CHEMOTHERAPY FOR PATIENTS WITH EARLY RELAPSING RECURRENT (INOPERABLE LOCALLY ADVANCED OR METASTATIC) TRIPLE-NEGATIVE BREAST CANCER**

PROTOCOL NUMBER: MO39193

STUDY DRUG: TECENTRIQ® (Atezolizumab)

VERSION NUMBER: 2

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SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: See electronic signature on the last page of this document.

STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document V1.0

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
Version 2	see electronic date stamp on the last page of this document	Version 8, 12 November 2021
Version 1	15 June 2022	Version 8, 12 November 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
4.4.4 Sensitivity Analyses	Addition of overall survival analysis in the Full Analysis Set population.	A plan for an overall survival sensitivity analysis based on the Full Analysis Set population has been added in accordance with Food and Drug Administration feedback received.

Additional minor changes have been made throughout to improve clarity and consistency.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse events
AESI	adverse events of special interest
BOR	best overall response
CBR	clinical benefit rate
CCOD	clinical cut-off date
C-DOR	duration of confirmed response
C-ORR	confirmed objective response rate
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CV	coefficient of variation
DOR	duration of response
DRB	Data Review Board
eBC	early Breast Cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5-Dimension 5-Level questionnaire
FACT-G	Functional Assessment of Cancer Therapy: General
FAS	full analysis set
FPI	first patient randomized
GHS	global health status
HGRAC	Human Genetics Resources Administration of China
HR	hazard ratio
HRQoL	health-related quality of life
iDMC	independent Data Monitoring Committee
iDCC	independent Data Coordinating Center
IHC	immunohistochemistry
IRBs/ECs	Institutional Review Boards/Ethics Committees
IV	Intravenous
IxRS	Interactive voice/web response system
LS Mean	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MID	minimally important difference
mITT	modified intent to treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPT	non-protocol therapy
ORR	objective response rate
OS	overall survival
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PT	preferred term
QLQ-BR23	Quality of Life Questionnaire breast cancer module
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	rank-preserving structural failure time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SE	standard error
SOC	system organ class
TAP	Tumor Area Positivity
TTCD	time to confirmed deterioration
TNBC	triple-negative breast cancer
ULN	upper limit of normal

1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the analyses that are planned to be performed for the Clinical Study Report (CSR) of Study MO39193 (IMpassion132).

2. STUDY DESIGN

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

Global Study: A total of approximately 572 patients will be randomized at a 1:1 ratio in the study. Before protocol amendment version 4.0, the study enrolled 382 patients with inoperable recurrent TNBC irrespective of programmed death-ligand 1 (PD-L1) tumor status (referred to as 'all-comers'). After protocol amendment version 4.0, approximately 190 additional patients with PD-L1(SP142)-positive tumor status will be further randomized, in order to reach approximately 330 patients with PD-L1(SP142)-positive tumor status required for the primary endpoint analysis of overall survival (OS) in the PD-L1(SP142)-positive population.

Additional Enrolment in China: After approximately 572 patients have been randomized in the Global study, global recruitment will be closed. Additional patients with PD-L1(SP142)-positive tumor status may be subsequently randomized in China only, following the same randomization procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1(SP142)-positive tumor status in China (including patients from China enrolled in the Global study), referred to as the China sub-population. The schedule of assessments and study treatments for these patients will be identical to those in the Global study, with the following exceptions: patients enrolled in China will not undergo plasma, whole blood, or optional tumor sample collections for exploratory biomarker assessments. Analyses based on the China sub-population will be performed and summarized separately.

The study schema is shown in Figure 1.

Figure 1 Study Schema

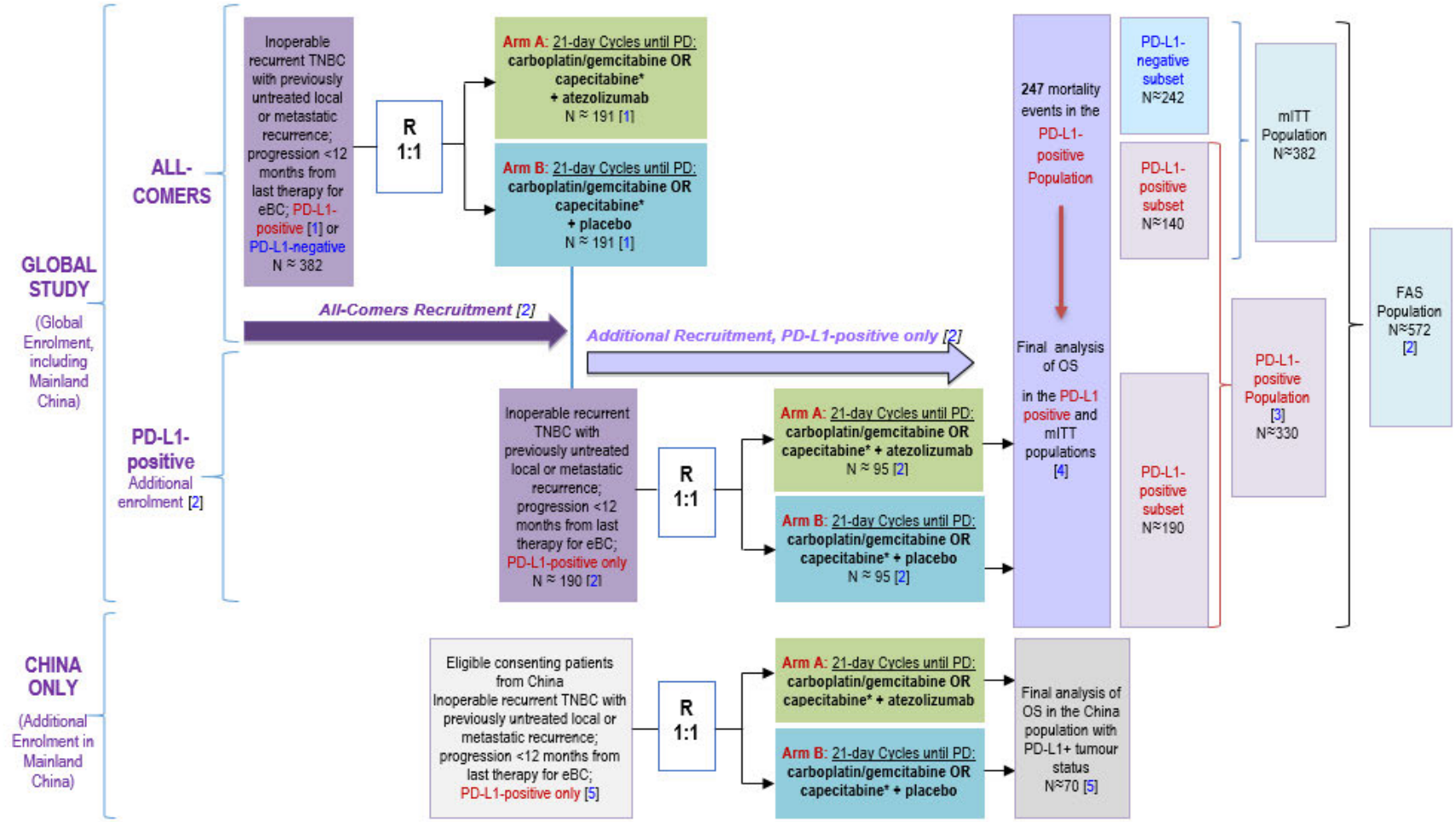


Figure 1 Study Schema (cont.)

eBC=early breast cancer; D =day; FAS=Full Analysis Set; IV=intravenous; mITT=modified Intent-to-Treat (population); N=number; OS=overall survival; PD=disease progression; R=randomization; PD-L1=programmed death-ligand 1; RECIST=Response Evaluation Criteria in Solid Tumors; TNBC=triple-negative breast cancer.
[1] Based on the 382 'all-comers' enrolled in the Global study, approximately 37% (N=140) of 'all-comer' patients have PD-L1(SP142)-positive tumor status.
[2] Following the enrolment of 382 'all-comers', approximately 190 additional patients with PD-L1(SP142)-positive tumor status will be randomized in a 1:1 ratio to receive atezolizumab with chemotherapy (Arm A) or placebo with chemotherapy (Arm B), for a total of approximately 572 patients randomized into the Global study (FAS).
[3] The PD-L1(SP142)-positive population (defined as all patients randomized in the study whose PD-L1 status was IC1/2/3 (as per SP142 assay) at the time of randomization) is the primary analysis population.
[4] No analysis is planned before the target number of OS events (247) is reached in the PD-L1(SP142)-positive population. OS in the mITT population will also be analyzed at that time.
[5] After approximately 572 patients have been randomized in the Global study (including patients from China), global recruitment will be closed. Additional patients with PD-L1(SP142)-positive tumor status may be subsequently randomized in China only, following the same randomization procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1(SP142)-positive tumor status in China (including patients enrolled in the Global study), referred to as the China sub-population.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2 and Appendix 3.

2.2 OUTCOME MEASURES

This study will evaluate the efficacy and safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy in patients with inoperable recurrent TNBC. Specific objectives and corresponding endpoints for the study are outlined in Table 1 below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy.	• Overall survival (OS), defined as time from randomization to death from any cause. OS will be tested hierarchically in the following fixed order: o In the population with programmed death-ligand 1 (PD-L1)-positive tumor status (as per SP142 assay), o In the modified intent-to-treat (mITT) population.
Secondary Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy.	• 12-month survival rate, defined as the proportion of patients alive 12 months after randomization. • 18-month survival rate, defined as the proportion of patients alive 18 months after randomization. • Progression-free survival (PFS), defined as the time from randomization to the first occurrence of

Table 1 Objectives and Corresponding Endpoints (cont.)

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives:	
	disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or death from any cause, whichever occurs first. PFS will be tested hierarchically in the following fixed order: o In the PD-L1(SP142)-positive population, o In the mITT population. • Objective response rate (ORR), defined as the proportion of patients with an unconfirmed objective response, defined as a complete response (CR) or a partial response (PR), as determined by the investigator according to RECIST 1.1. ORR will be tested hierarchically in the following fixed order: o In the PD-L1(SP142)-positive population, o In the mITT population. • Duration of objective response (DoR), defined as the time from the first occurrence of a documented unconfirmed objective response to disease progression, as determined by the investigator according to RECIST 1.1, or to death from any cause, whichever occurs first. • Clinical benefit rate (CBR), defined as the proportion of patients with a CR or a PR, or stable disease (SD) that lasts ≥ 6 months, as determined by the investigator according to RECIST 1.1. • In addition, confirmed objective response rate (C-ORR) and duration of confirmed response (C-DoR) will be analysed.
• To evaluate patient-reported outcomes (PROs) of global health status (GHS)/ quality of life (QoL) associated with atezolizumab plus chemotherapy compared with placebo plus chemotherapy, as measured by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).	• Time to confirmed deterioration (TTCD) of GHS/QoL, defined by a minimally important decrease of ⩾10 points at two consecutive assessment time-points on the GHS/QoL scale (Items 29, 30) of the EORTC QLQ-C30.

Table 1 Objectives and Corresponding Endpoints (cont.)

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

Table 1 Objectives and Corresponding Endpoints (cont.)

• Objectives	• Corresponding Endpoints
Specific Efficacy Objectives for Patients Recruited in China (Cont.):	
efficacy observed in the Global population (Global study).	
Safety Objectives:	
• To evaluate the safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy.	• Incidence, nature and severity of adverse events (AEs), with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). • Change from baseline in targeted vital signs Change from baseline in targeted clinical laboratory test results.
Pharmacokinetics Objectives:	
• To characterize the pharmacokinetics (PK) of atezolizumab when administered with carboplatin/gemcitabine or with capecitabine.	• Peak and trough of atezolizumab concentrations in serum (C_{max} and C_{min}) at specified time points during treatment.
Immunogenicity Objective:	
• To evaluate the immunogenicity of atezolizumab.	• Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline.
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs.	• Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objectives:	
• To assess the efficacy and safety of atezolizumab plus chemotherapy according to PD-L1 status.	• Relationship between PD-L1 protein expression by immunohistochemistry (Ventana® PD-L1 SP142 IHC assay) in screening tumor tissue and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC1/2/3).
Exploratory Biomarker Objectives:	
• To assess the efficacy and safety of atezolizumab plus chemotherapy according to PD-L1 status using a second PD-L1 assay.	• Relationship between PD-L1 positive population according to Ventana SP263 at the Tumor Area Positivity (TAP) 5% and 10% and efficacy endpoints (OS and PFS).

Table 1 Objectives and Corresponding Endpoints (cont.)

ADAs = anti-drug antibodies; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-G = functional assessment of cancer therapy: general; mITT = modified intent-to-treat; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = Progression-free survival; PK = pharmacokinetics; PROs = patient-reported outcomes; RECIST = response evaluation criteria in solid tumors.

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

2.3 DETERMINATION OF SAMPLE SIZE

2.3.1 Global Study

The purpose of this event-driven study is to evaluate the efficacy of atezolizumab plus chemotherapy versus placebo plus chemotherapy in patients with early-relapsing (< 12 months) inoperable recurrent TNBC as measured by OS.

In order to control for the overall type I error at two-sided 5%, the primary OS endpoint will be evaluated hierarchically in the following fixed order: (1) OS in the PD-L1(SP142)-positive population, followed by (2) OS in the mITT population.

Based on the estimated median OS of 9 months in the control arm (assuming a similar median OS in the PD-L1(SP142)-positive and mITT populations based on available data), and a 1:1 randomization ratio, 247 OS events are required to detect a target hazard ratio (HR) of 0.70 (3.8-month improvement in median OS) with the addition of atezolizumab to chemotherapy, with 80% power by two-sided log-rank test at an alpha level of 0.05. The expected study recruitment rate is approximately 20 all-comer patients per month. Of the 382 'all-comers' enrolled in the Global study, approximately 37% (N = 140) were found to have PD-L1(SP142)-positive tumor status. Subsequent recruitment will continue only in patients with PD-L1(SP142)-positive tumor status, for approximately 190 additional patients randomized, in order to achieve the target sample size of 330 patients and the required 247 events for the primary OS analyses in the PD-L1(SP142)-positive population.

The overall study population is estimated at approximately 572 patients (382 all-comers plus approximately 190 additional patients with PD-L1(SP142)-positive tumor status).

Refer to Table 2 for further details.

Table 2 Operating Characteristics

Sample Size Calculation Parameters	Values	
	PD-L1(SP142)-positive Population [1]	**mITT Population** [2]
Randomization ratio (atezolizumab + chemotherapy vs. placebo+chemotherapy)	1:1	
Expected median OS, Control arm	9 months	
Target HR (hazard ratio), of atezolizumab + chemotherapy vs. placebo+chemotherapy	0.7	
Type 1 error (2-sided)	5%	
Power	80%	~ 87%
Recruitment period	~ 53 months [3]	~ 23 months
Follow-up time after the last patient is randomised	~ 5 months	~35 months
Assumed drop-out rate	10%	
Number of primary endpoint (OS) events	247 [4]	~ 297 [4]
Minimal Detectable Difference (MDD)	HR≤0.779	HR≤0.797
Duration until primary OS analysis	~ 58 months [4]	
Number of patients	~ 330	~ 382
Total sample size in the study	~ 572 patients (382 all-comers (mITT) plus ~ 190 additional PD-L1(SP142)-positive patients)	

HR=hazard ratio; mITT=modified Intent-to-Treat; OS=overall survival; PD-L1=programmed death-ligand 1.

[1] The PD-L1(SP142)-positive population includes all patients randomized in the study (before and after protocol version 4.0) whose PD-L1 status was IC1/2/3 by SP142 assay at the time of randomization.

[2] The mITT population includes all patients randomized in the study before protocol version 4.0 (PD-L1[SP142]-positive and PD-L1[SP142]-negative).

[3] Including the 23-month recruitment period for all-comers.

[4] The clinical cut-off date for the primary endpoint analysis will take place when the required number of 247 mortality events have been reported in the PD-L1(SP142)-positive population (projected to occur approximately 58 months after FPI). By this time-point, approximately 297 mortality events are expected to have occurred in the mITT population under the study clinical assumptions, but actual number may vary given the primary analysis is driven by the number of events in by PD-L1(SP142)-positive population.

Note: Calculations were conducted in R version 1.9.1.

2.3.2 Controlling for Type I Error

All tests will be performed at two-sided alpha of 5% with testing for the primary and secondary endpoints conducted hierarchically, using a fixed sequence testing approach (Westfall and Krishen 2001), where each subsequent hypothesis will be tested only if all previously tested hypotheses have been rejected, according to the following pre-specified and fixed order of endpoints:

Primary endpoint:

1. OS (PD-L1[SP142]-positive population)
2. OS (mITT population)

Secondary endpoints:

1. PFS by RECIST v1.1 (PD-L1[SP142]-positive population)
2. PFS by RECIST v1.1 (mITT population)
3. ORR by RECIST v1.1 (Response-evaluable population subset of the PD-L1[SP142]-positive population)
4. ORR by RECIST v1.1 (Response-evaluable population subset of the mITT population)

The remaining secondary endpoints (12-month and 18-month OS rates, TTCD in the GHS/QoL, DOR, CBR, as well as C-ORR and C-DOR) will not be adjusted for multiple testing.

2.3.3 China Sub-Population

After approximately 572 patients have been randomized in the Global study, global recruitment will be closed. Additional patients with PD-L1(SP142)-positive tumor status might be subsequently randomized in China only, following the same randomization procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1(SP142)-positive tumor status in China (including patients enrolled in the Global study). The sample size of the China sub-population was determined by characterizing the efficacy and safety profile of atezolizumab combined with chemotherapy.

2.4 ANALYSIS TIMING

The clinical cutoff date (CCOD) date for the primary analysis of OS will take place when the required number of 247 OS events have been observed in the PD-L1(SP142)–positive population. At this same time, OS in the mITT population may also be formally statistically tested, as well as PFS and ORR in both the PD-L1(SP142)–positive population and mITT population, according to the pre-specified hierarchical testing (see Section 2.3.2).

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

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization to atezolizumab plus chemotherapy or placebo plus chemotherapy will occur in a 1:1 ratio using a permuted-block randomization method. The randomization will be stratified on the following factors:

- Presence of visceral (lung and/or liver) metastases (yes vs. no)
- Tumor PD-L1 status (IC0 vs. IC1/2/3) (only for protocol versions prior to 4.0)
- Chemotherapy choice (carboplatin/gemcitabine vs. capecitabine)

3.2 INDEPENDENT REVIEW FACILITY

Imaging data used for tumor assessment may be retrospectively collected by the Sponsor to enable centralized, independent review of response endpoints by an Independent Review Committee in the future, if necessary.

3.3 DATA MONITORING

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 unblinding to review study conduct and unblinded safety data prepared by an independent Data Coordinating Center (iDCC).

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 study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

Details are specified in the iDMC Charter.

4. STATISTICAL METHODS

The analyses outlined in this SAP supersede those specified in the protocol for the purpose of a regulatory filing.

4.1 ANALYSIS POPULATIONS

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

- Full Analysis Set (FAS) population: all patients randomized in the study, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- Modified ITT (mITT) population: all patients randomized under the protocol versions prior to version 4.0 (referred to as all-comers, i.e., PD-L1(SP142)-positive and PD-L1(SP142)-negative patients), grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- PD-L1(SP142)–positive population: all patients randomized in the study whose PD-L1 status was IC1/2/3 by SP142 assay at the time of randomization, grouped according to their assigned treatment arm, whether or not the assigned study treatment was received.
- Response-evaluable population: patients randomized in the study with measurable disease at baseline.
- DOR-evaluable population: patients randomized in the study with measurable disease at baseline and an objective response.
- C-DOR-evaluable population: patients randomized in the study with measurable disease at baseline and a confirmed objective response.
- Safety-evaluable population: patients who received any amount of any study drug (atezolizumab/placebo or chemotherapy).
- Pharmacokinetic (PK)-evaluable population: patients who received any dose of study medication and who have at least one evaluable post-baseline PK sample.
- Anti-drug antibody (ADA) population:
  - Baseline ADA-evaluable population: All patients with at least one evaluable ADA assay result from a baseline sample.
  - Post-baseline ADA-evaluable population: All patients with at least one evaluable ADA assay result from at least one post-baseline sample.

For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

For all safety, PK, and immunogenicity analyses, patients will be grouped according to the treatment actually received, including cases in which atezolizumab was received in error.

If a patient has been randomized more than once, he/she will be kept once and be assigned as per his/her last randomization.

China sub-population is defined as all patients enrolled in China coming from the global cohort and from the additional enrolment.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrolment, patient disposition, reason for discontinuation from study treatment, reason for study termination, and number of patients unblinded will be summarized for patients in the PD-L1(SP142)-positive population and mITT population, as well as in the FAS population when relevant.

Major protocol deviations, including violations of inclusion/exclusion criteria and deviations during study conduct, as well as major protocol deviations related to COVID-19 will be reported and summarized for patients in the PD-L1(SP142)-positive population and mITT population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The following analyses will be based on the PD-L1(SP142)–positive population and mITT population.

Demographic variables such as age, sex, race/ethnicity, stratification variables, and other relevant baseline characteristics will be summarized using means, standard deviations (SDs), medians, ranges, and interquartile ranges for continuous variables and frequencies and percentages for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm.

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. The baseline value of efficacy variable related to tumor assessment will be defined as the last available value recorded prior to randomization. Baseline value will be data reported at Cycle 1, Day 1 for EORTC (QLQ-C30 and QLQ-BR23) questionnaires.

Previous and concurrent medical history will be summarized overall and by treatment arm.

Prior systemic cancer therapy, prior cancer surgery, prior cancer radiotherapy, on-study cancer surgery, on study cancer radiotherapy, follow-up systemic cancer therapy, anti-cancer therapies administered after progression, anti-cancer therapies administered before progression or for patients with no progression, follow-up cancer surgery, follow-up cancer radiotherapy will be summarized overall and by treatment arm.

Therapies considered as treatment switching will also be summarized overall and by treatment arm. Treatment switching therapies are anti–PD-1 or anti–PD-L1 immunotherapies.

4.4 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be performed for the PD-L1(SP142)–positive population and the mITT population, unless specified otherwise.

Hypothesis tests will be two-sided unless otherwise indicated. The overall type I error (α) for this study is 5%.

4.4.1 Primary Efficacy Endpoint

OS is defined as the time from randomization to death due to any cause. Patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization + 1 day.

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

1. OS in the PD-L1(SP142)–positive population, followed by
2. OS in the mITT population.

A confirmatory test on (2) will only be conducted if the null-hypothesis for (1) has been rejected at a two-sided 5% significance level.

The following analyses will be performed:

- Treatment comparisons will be based on the stratified log-rank test. The stratification factors will be the pre-defined randomization stratification factors: presence of visceral (lung and/or liver) metastases (yes vs. no), tumor PD-L1 status (IC0 vs. IC1/2/3 as per SP142 assay, for analyses on mITT only), chemotherapy choice (carboplatin/gemcitabine vs. capecitabine) and will be obtained from the interactive Web/phone response system (IxRS). Results from an unstratified analysis will also be provided.
- The HR 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
- Kaplan-Meier methodology will be used to estimate median OS 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 OS for each treatment arm (Brookmeyer and Crowley 1982).

4.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- 12-month survival rate, in the PD-L1(SP142)-positive population and the mITT population
- 18-month survival rate, in the PD-L1(SP142)-positive population and the mITT population
- PFS, in the PD-L1(SP142)-positive population and the mITT population
- ORR by investigator assessment using RECIST v1.1, assessed in the response-evaluable population subset of the PD-L1(SP142)-positive population and of the mITT population

- DOR, by investigator assessment using RECIST v1.1, in the DOR-evaluable population subset of the PD-L1(SP142)-positive population and of the mITT population
- CBR, by investigator assessment using RECIST v1.1, in the response-evaluable population subset of the PD-L1(SP142)-positive population and of the mITT population
- Time to confirmed deterioration (TTCD) in Global Health Status/QoL (Items 29, 30 of the EORTC QLQ-C30), in the PD-L1(SP142)-positive population and the mITT population
- Confirmed ORR (C-ORR), by investigator assessment using RECIST v1.1, assessed in the response-evaluable population subset of the PD-L1(SP142)-positive population and of the mITT population
- Confirmed DOR (C-DOR) by investigator assessment using RECIST v1.1, assessed in the C-DoR–evaluable population subset of the PD-L1(SP142)-positive population and of the mITT population

The following endpoints will be tested hierarchically at an overall study-level two-sided alpha of 5%, 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[SP142]-positive population)
2. PFS by RECIST v1.1 (mITT population)
3. ORR by RECIST v1.1 (Response-evaluable population subset of the PD-L1[SP142]-positive population)
4. ORR by RECIST v1.1 (Response-evaluable population subset of the mITT population).

The remaining secondary endpoints (12-month and 18-month OS rates, DOR, CBR, as well as C-ORR and C-DOR) will not be adjusted for multiple testing.

4.4.2.1 Overall Survival Rate at 12 and 18 Months

OS rate at 12 and 18 months will be estimated for each treatment arm using Kaplan-Meier methodology, along with 95% CI calculated with the standard error (SE) derived from the Greenwood formula. The 95% CIs for the difference in OS rates between the two arms will be estimated using the normal approximation method.

4.4.2.2 Progression-Free Survival

PFS is defined as the time from randomization to the first occurrence of disease progression as determined by the investigator from tumor assessments using RECIST v1.1 or death from any cause during the study, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored i) at the time of the last tumor assessment if there is a post-baseline tumor

assessment or ii) on the date of randomization + 1 day if there is no post-baseline tumor assessment.

PFS will be analyzed hierarchically in the following fixed order:

1. PFS in the PD-L1(SP142)-positive population followed by
2. PFS in the mITT population.

Testing on PFS will be conducted hierarchically only if the null hypothesis for testing on OS has been rejected.

Analysis of PFS will be completed using the same methods as described for the primary endpoint (OS).

4.4.2.3 Best Overall Response

The best overall response (BOR) for a patient is defined as the most favorable outcome, on the basis of investigator assessment using RECIST v1.1 criteria, at any visit after randomization and up to the first documented disease progression. Confirmation of response is not required.

Patients will be classified as "stable disease" if assessment is at least 7 weeks from baseline. Patients will be classified as “missing or unevaluable” if no post-baseline response assessment is available or if all post-baseline response baseline assessments are unevaluable.

BOR will be analyzed using the response-evaluable population subset of the PD-L1(SP142)-positive population and response-evaluable population subset of the mITT population and will be summarized by treatment arm.

4.4.2.4 Objective Response Rate

An objective response is defined as 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 tumor assessment, will be considered as non-responders.

ORR is defined as the proportion of patients who have an objective response. ORR will be analyzed using the response-evaluable population subset of the PD-L1(SP142)-positive population and response-evaluable population subset of the mITT population.

ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint of OS. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the

normal approximation to the binomial distribution. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method.

C-ORR will also be analyzed. Confirmed response will be calculated using the next scheduled scan, at least 4 weeks apart. It is acknowledged that this may underestimate the true confirmed response rate compared to the Eisenhauer (2009) criteria.

C-ORR is defined as the proportion of patients with measurable disease at baseline who achieved a documented confirmed response (CR or PR) at the next scheduled scan on the basis of investigator assessment using RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumor assessment, will be considered as non-responders. C-ORR will be analyzed using the response-evaluable population subset of the PD-L1(SP142)-positive population and the response-evaluable population subset of the mITT population. Similar analyses as for ORR will be performed.

4.4.2.5 Duration of Response

DOR is defined as the time from the first occurrence of a documented unconfirmed response (CR or PR) until the date of disease progression as determined by the investigator from tumor assessments using RECIST v1.1 or death from any cause, whichever occurs first. DOR will be analyzed in the DOR-evaluable population subset of the PD-L1(SP142)-positive population and DOR-evaluable population subset of the mITT population.

Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. If no tumor 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-randomized 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 OS will be used for the analysis of DOR except that the analysis will not be stratified.

Similar to C-ORR, C-DOR will also be analyzed. Confirmed response will be calculated using the next scheduled scan, at least 4 weeks from the response scan.

C-DOR is defined as the time from the first occurrence of a documented confirmed response (CR or PR) until the date of disease progression per RECIST v1.1 or death from any cause, whichever occurs first. C-DOR will be analyzed in the C--DOR-evaluable population subset of the PD-L1(SP142)-positive population and

C-DOR-evaluable population subset of the mITT population. Similar analyses as for DOR will be performed.

4.4.2.6 Clinical Benefit Rate

CBR, 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, will be described by treatment arm. CBR will be analyzed using the same methods as described for ORR.

4.4.2.7 Time to Confirmed Deterioration in Global Health Status/ Quality of Life

Time to confirmed deterioration (TTCD) in GHS/ QoL will be analyzed based on data from the GHS/QoL scale of the EORTC QLQ-C30 in the PD-L1(SP142)-positive population and the mITT population.

Confirmed deterioration in GHS/QoL (Items 29, 30 of the EORTC QLQ-C30) is defined by the following two criteria:

1. The time from randomization to the first time the patient's GHS/QoL scale score shows a ≥10-point decrease from the baseline scale score. A 10-point change is defined as the minimally important difference (MID) (Osoba et al. 1998).
2. The score decrease of ≥10-points from baseline must be held for at least two consecutive cycles or an initial score decrease of ≥10-points is followed by death or treatment discontinuation within 3 weeks from the last assessment.

TTCD in GHS/QoL will be compared between the treatment groups using the same method as the primary endpoint of OS. Patients who have not deteriorated before the last PRO assessment is completed will be censored at the time the last GHS/QoL data are available.

In addition, the impact of non-protocol therapy (NPT) on the PRO endpoint of TTCD in GHS/QoL might be evaluated in patients who completed the PRO assessments. If deemed relevant, a sensitivity analysis might be performed in which data for patients who received NPT will be censored at the last PRO assessment date before receiving NPT.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 Changes from Baseline in Patient Function and Symptoms EORTC (QLQ-C30 and QLQ BR23) Data

PRO data from the EORTC QLQ-C30 and QLQ-BR23 will be analyzed based on the PD-L1(SP142)-positive population and the mITT population, unless specified otherwise.

Summary statistics (mean, 95%CIs, median, and range) of linearly transformed 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. The mean change from baseline (and 95% CI) will be assessed to further inform TTCD in HRQoL and of patients' treatment experience. 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-confirmed-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. This will follow the same approach as used for the GHS/QoL scale.

Deterioration in function will be assessed using the published corresponding MIDs (Osoba et al. 1998; Cocks et al. 2011). Patients who do not achieve an MID based on published thresholds will be censored at the time the last EORTC QLQ-C30 subscale data are available if baseline and post-baseline subscale assessments exist. A stratified and unstratified 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, age group, ECOG performance status and brain metastases at baseline) 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% CI for the differences. The 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). Missing data will be assessed and reported by timepoint. 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, and reasons for missing data will be summarized at each timepoint by treatment arm for the PD-L1(SP142)–positive population and for the mITT population.

4.4.3.2 Treatment Side-Effects Bother—FACT-G Single Item GP5 Data

The bother of treatment side-effects associated with the addition of atezolizumab to chemotherapy 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 5-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 the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported using the PD-L1(SP142)-positive population and the mITT population. Additionally, the proportion of patients reporting improvement,

deterioration or no change in symptoms following the first assessment will be provided. Graphical representation of FACT-G GP5 data over time will also be provided.

4.4.3.3 Health Economic Data

Health economic data will be assessed by the EQ-5D-5L. The results from the health economic data analysis will be reported separately from the CSR.

4.4.4 Sensitivity Analyses

4.4.4.1 Sensitivity Analyses of Overall Survival

Mis-stratification

The analysis on OS will be repeated by using the stratification factors based on the eCRF as sensitivity analyses, if at least 10% of discrepancies between IxRS versus CRF/Laboratory data.

Accounting for Second-Line Immunotherapy Use

Quickly evolving development of checkpoint inhibitors may lead to increased PD-L1/PD-1 treatment options for patients in second-line TNBC, either via trial participation or newly approved medicines in this class. Second-line usage of such inhibitors by patients progressing on this first-line trial could result in a biased estimate of the treatment effect on OS (of note, unblinding upon disease progression as per RECIST 1.1 was allowed as per protocol). To account for this possibility of bias, the following sensitivity analyses will be conducted.

- **Censoring for Treatment Switching**

  Treatment switching is defined as any checkpoint inhibitor therapy other than study treatment as a subsequent line of therapy (see Section 4.3). A sensitivity analysis will be performed in which data for patients who received treatment switching will be censored at the date the patient received treatment switching.

- **Rank-Preserving Structural Failure Time Method**

  The rank-preserving structural failure time (RPSFT) method was introduced by Robins and Tsiatis (1991). It provides an estimate of the OS time for the placebo arm had treatment switching not occurred. It estimates OS time measured from the time of treatment switching by applying an estimate of the benefit of the atezolizumab treatment (derived iteratively and referred to as the inverse of the acceleration factor). The adjusted OS time (sum of time to switching and the estimated survival time after switching) will then be analyzed together with the OS times of the patients who did not switch by using the same methodology as for the primary analysis of OS, provided there is a sufficient number of treatment switching.

Centrally Confirmed TNBC Testing

The analysis on OS will be repeated on patients having centrally confirmed TNBC status as sensitivity analysis.

Full Analysis Set

As a sensitivity analysis, the analysis of OS will be repeated in the FAS population.

4.4.4.2 Sensitivity Analyses of Progression-Free Survival Mis-stratification

The analysis on PFS will be repeated by using the stratification factors based on the eCRF as a sensitivity analysis, if at least 10% of discrepancies between IxRS versus CRF/Laboratory data.

Missing Tumor Assessment

The impact of missing scheduled tumor assessments on the investigator-assessed PFS by RECIST v1.1 will be evaluated. A sensitivity analysis will be performed in which data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

Censoring for Non-Protocol Therapy

NPT is defined as any anti-cancer therapy other than study treatment that typically is the subsequent line of therapy (as reported on the "Follow-Up Cancer Therapy Assessment" eCRF page). The impact of NPT on PFS by RECIST v1.1 will be evaluated.
A sensitivity analysis will be performed in which data for patients who received NPT will be censored at the last tumor assessment date on or before the patient received NPT.

Centrally Confirmed TNBC Testing

The analysis on PFS will be repeated on patients having centrally confirmed TNBC status as sensitivity analysis.

4.4.5 Subgroup Analyses

To assess the consistency of study results across subgroups, OS and PFS will be evaluated in the following subgroups:

- PD-L1 status (as per SP142 assay)
- Chemotherapy type subgroup (carboplatin/gemcitabine vs. capecitabine)
- Baseline characteristics: age group, race, baseline ECOG performance status,
- Disease involvement: presence of visceral (lung and/or liver) metastases (per eCRF), brain metastases, nodal disease only, bone metastases, baseline disease status, number of sites
- Disease history: prior anthracycline treatment, prior taxane treatment, prior platinum treatment, prior therapy, time from last curative-intent surgery until diagnosis with metastatic or locally advanced unresectable disease, median time from initial diagnosis until local advanced unresectable or metastatic disease, chemotherapy-free interval

Summaries of OS and PFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median, will be produced separately for each level of the categorical variables. Forest plots will be used to summarize the results on the PD-L1(SP142)-positive population and the mITT population.

Subgroups analysis for ORR will also be performed by PD-L1 status (as per SP142 assay). Summaries of ORR, including odds ratio obtained from the unadjusted logistic regression and response rates, will be produced separately for each level of the categorical variables. Forest plots will be used to summarize the results on the response-evaluable population subset of the PD-L1(SP142)-positive population and response-evaluable population subset of the mITT population.

A subgroup analysis of TTCD in GHS/QoL will also be conducted for each chemotherapy type subgroup (i.e., carboplatin/gemcitabine and capecitabine groups) on the PD-L1(SP142)-positive population and the mITT population.

4.5 PHARMACOKINETIC ANALYSES

All PK analyses will be performed on the PK-evaluable population.

Sparse serum atezolizumab concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, geometric mean, ranges, SDs, and %CV, or others as appropriate.

PK by ADA will be presented graphically by box plots with individual distributions. A corresponding descriptive statistic table will also be provided.

Additional PK analyses may be conducted if deemed appropriate.

4.6 SAFETY ANALYSES

All safety analyses will be performed on the safety-evaluable population subset of FAS, unless specified otherwise.

4.6.1 Exposure of Study Medication

Study treatment (atezolizumab/placebo, carboplatin/gemcitabine or capecitabine) exposure, including treatment duration, dose intensity, number of cycles received, total cumulative dose and number of missed doses, will be summarized with descriptive statistics by treatment arm.

4.6.2 Adverse Events

Verbatim description of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and preferred term [PT]), and when

specified, by NCI CTCAE grade. For each patient, if multiple incidences of the same AEs occur, the maximum severity reported will be used in the summaries. Only AEs occurring on or after the first dose of any study treatment will be included in the summary tables of AEs. Adverse events occurring prior the first dose of any study treatment will be summarized separately as "baseline signs and symptoms."

Summary tables by treatment group will include but are not limited to the following:

- AEs
- AEs by highest NCI CTCAE grade,
- Serious adverse events (SAEs)
- SAEs by highest NCI CTCAE grade
- SAEs related to i) any study treatment, ii) atezolizumab/placebo
- Grade 3–4 AEs
- AEs leading to discontinuation of i) any study treatment, ii) atezolizumab/placebo,
- AEs leading to dose reduction or interruption of i) any study treatment, ii) atezolizumab/placebo,
- AEs resulting in death
- AEs related to i) any study treatment, ii) atezolizumab/placebo,
- Adverse Events of Special Interest (AESIs) (for the purpose of analysis, a set of comprehensive definitions comprising Sponsor-defined, standardized MedDRA queries [SMQ], high-level terms [HLTs], and Sponsor-defined AE Grouped Terms [AEGTs] will be used to identify and summarize AESIs by medical concept. The medical concepts include atezolizumab-associated identified risks, potential risks and class effects reported with other immune-checkpoint inhibitors).
- AESIs requiring use of systemic corticosteroids
- Overview safety summary table of the safety-evaluable population subset of PD-L1(SP142)-positive population

All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the CCOD.

AEs associated with COVID-19 will be listed. Confirmed or suspected COVID-19 AEs, as well as AEs associated with COVID-19 will be summarized by treatment arm. Same analyses will be repeated for SAEs. Further analyses might be added, if deemed relevant.

All deaths and causes of deaths will be summarized by treatment arm.

4.6.3 Laboratory Data

Laboratory data will be summarized descriptively over time, including change from baseline by treatment arm.

Laboratory data will be classified according to NCI CTCAE v4.0. Highest NCI CTCAE grade post-baseline will also be reported, and shift tables from baseline to worst post-baseline will be presented by treatment arm.

Potential Hy's law patients will be listed. Potential Hy's law cases are defined as elevated ALT or AST ($>3\times$upper limit of normal [ULN]), with concomitant elevated total bilirubin ($>2\times$ULN).

4.6.4 Anti-Drug Antibodies

ADA analyses will be performed using the post-baseline ADA-evaluable population.

Patients will be classified as treatment-emergent ADA positive if they were ADA negative at baseline or missing data but developed an ADA response following study drug administration (treatment-induced ADA response) or if they were ADA positive at baseline and the titre of one or more post-baseline samples was 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 post-baseline ADA negative if they were ADA negative or missing data at baseline and all post-baseline samples were negative or if they were ADA positive at baseline but did not have any post-baseline samples with a titre that was 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 summarized by treatment arm and listed by patient and cycle.

Exploratory descriptive analyses of baseline characteristics, exposure, efficacy, and safety by ADA status may be performed.

4.6.5 Vital Signs and ECOG Performance Status

For vital signs and ECOG performance status, a shift table from baseline versus worst post-baseline will be presented by treatment arm.

4.6.6 Electrocardiograms

The baseline ECG of the patients will be summarized and results of on-study ECGs will be listed.

4.7 BIOMARKERS ANALYSES

To evaluate the dependency of the action of the drug combination (atezolizumab plus chemotherapy) according to prospectively determined PD-L1 expression, analyses of the relationship between PD-L1 status by immunohistochemistry (IHC; PD-L1-positive IC1/2/3 vs. PD-L1-negative IC0 as per SP142 assay) and clinical efficacy and safety outcomes will be undertaken.

4.7.1 Exploratory Biomarker Analyses

The relationship between VENTANA SP263 assay and its predictive effect on key efficacy endpoints (PFS and OS) will be investigated on the FAS population using two pre-specified TAP thresholds to define subpopulations (TAP $\geq$5% and TAP $\geq$10%). No formal statistical testing will be carried out on the analyses.

With the exception of SP142 PD-L1 data (stratification factor for protocol versions prior to 4.0), results of biomarker analyses will not be included in the CSR.

Patients enrolled in China will only be included in exploratory biomarker analyses that are based on mandatory tumor tissue samples collected at screening.

In December 2017 and August 2018, Ventana Medical Systems recalled multiple detection kits used for IHC laboratory testing due to the leaking and sticking of reagent dispensers, which could cause false negative results. Available samples from patients enrolled in IMpassion132 tested with impacted dispenser lots were retested by the same external central laboratory that performed the original staining. Analyses of test/retest samples for PD-L1 status and TNBC status will be performed, as well as sensitivity analysis for OS and PFS if relevant.

4.8 MISSING DATA

See Section 4.4.1 and Section 4.4.2 for methods of handling missing data for the primary and secondary efficacy endpoints.

4.9 INTERIM ANALYSES

4.9.1 Planned Interim Analysis

No interim analyses of efficacy are planned.

4.9.2 Safety Monitoring

The iDMC will review the safety data periodically during the study.

Full details are provided in the iDMC Charter.

4.9.3 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.

5. CHINA SUBGROUP ANALYSIS

The China subgroup analysis will be conducted in the China subpopulation, including Chinese patients enrolled in the global cohort and the additional enrolment, Section 4. The timing of the China subgroup analysis depends on the data maturity and pre-specified number of OS events from the China subpopulation.

Analyses of study conduct will be performed as described in Section 4.2. Summaries of demographics, disease history, baseline disease characteristics, and patient treatment history will be produced as described in Section 4.3. Analyses of the primary efficacy endpoint, OS, will be performed analogous to patients from global cohorts, as described in Section 4.4.1.

Safety data for the China subpopulation will be analyzed as described in Section 4.6.

The analysis of other endpoints will use the same methods for global cohorts but with exploratory purpose only.

6. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Cella D. The Functional Assessment of Cancer Therapy-Anemia (FAXCT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol. 1997;34(3 Suppl 2):13-9.

Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. J Clin Oncol 1993; 11:570-79.

Cocks K., King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011;29:89-96.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

Fayers PM, Aaronson NK, Bjordal K, et al. on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 scoring manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality of life score. J Clin Oncol 1998;16:139-44.

Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communications in Statistics-Theory and Methods 1991;20(8):2609-31.

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference 2001; 99:25–41.

Appendix 1
Protocol Synopsis

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF ATEZOLIZUMAB PLUS CHEMOTHERAPY FOR PATIENTS WITH EARLY RELAPSING RECURRENT (INOPERABLE LOCALLY ADVANCED OR METASTATIC) TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	MO39193
VERSION NUMBER:	8.0
EUDRACT NUMBER:	2016-005119-42
IND NUMBER:	123277
TEST PRODUCT:	Atezolizumab (RO5541267, MPDL3280A)
PHASE:	Phase III
INDICATION:	Triple-negative breast cancer (TNBC)
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

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

Table 1 Study Objectives and Corresponding Endpoints

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

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives:	
• To evaluate the efficacy of atezolizumab plus chemotherapy compared to placebo plus chemotherapy	• 12-month survival rate, defined as the proportion of patients alive 12 months after randomization • 18-month survival rate, defined as the proportion of patients alive 18 months after randomization • Progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or death from any cause, whichever occurs first. PFS will be tested hierarchically in the following fixed order: o In the PD-L1-positive population, as defined in Section 6; o In the mITT population, as defined in Section 6. • Objective response rate (ORR), defined as the proportion of patients with an objective response, defined as a complete response (CR) or a partial response (PR), as determined by the investigator according to RECIST 1.1. ORR will be tested hierarchically in the following fixed order: o In the PD-L1-positive population, as defined in Section 6; o In the mITT population, as defined in Section 6. • Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST 1.1, or to death from any cause, whichever occurs first • Clinical benefit rate (CBR), defined as the proportion of patients with a CR or a PR or stable disease (SD) that lasts $\geqslant$ 6 months, as determined by the investigator according to RECIST 1.1.

Objectives	Corresponding Endpoints
	In addition, confirmed objective response rate (C-ORR) and duration of confirmed response (C-DOR) will be analysed. Details will be provided in the Statistical Analysis Plan (SAP).
• To evaluate patient-reported outcomes (PROs) of global health status (GHS)/quality of life (QoL) associated with atezolizumab plus chemotherapy compared with chemotherapy alone, as measured by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)	• Time to confirmed deterioration (TTCD) of GHS/QoL, defined by a minimally important decrease of ⩾10 points at two consecutive assessment time-points on the GHS/QoL scale (Items 29, 30) of the EORTC QLQ-C30
Exploratory Efficacy Objectives:	
• To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab plus chemotherapy compared with placebo plus chemotherapy, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23)	• Mean and mean changes from baseline in function (role physical, emotional, social, cognitive) and disease/treatment-related symptoms by treatment cycle, as assessed by the function scales and all symptom items/scales of the EORTC QLQ-C30 and the QLQ-BR23
• To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to chemotherapy compared with placebo plus chemotherapy, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical wellbeing subscale of the Functional Assessment of Cancer Therapy: General (FACT-G) quality of life instrument	• Proportion of patients reporting each response option at each assessment time point for item GP5 from the FACT-G
• To evaluate health utility as measured by the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire, to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L questionnaire

Objectives	Corresponding Endpoints
Specific Efficacy Objectives for Patients Recruited in China:	
• The objective of the China sub-population analyses is to evaluate whether the efficacy of atezolizumab plus chemotherapy compared with placebo plus chemotherapy as measured by OS and other efficacy endpoints in the China sub-population (enrolled in the Global study and during additional recruitment in China) is consistent with the efficacy observed in the Global population (Global study).	• As described for the Global study
Safety Objectives:	
• To evaluate the safety of atezolizumab plus chemotherapy compared with placebo plus chemotherapy	• Incidence, nature and severity of adverse events (AEs), with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE 4.0) • Change from baseline in targeted vital signs and physical findings • Change from baseline in targeted clinical laboratory test results
Pharmacokinetics Objectives:	
• To characterize the pharmacokinetics (PK) of atezolizumab when administered with carboplatin/gemcitabine or with capecitabine in patients with breast cancer	• Peak and trough of atezolizumab concentrations in serum (C_{max} and C_{min}) at specified time points during treatment
Immunogenicity Objective:	
• To evaluate the immunogenicity of atezolizumab	• Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline.
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objectives:	
• To assess the efficacy and safety of atezolizumab plus	• Relationship between PD-L1 protein expression by immunohistochemistry

Objectives	Corresponding Endpoints
chemotherapy according to programmed death−ligand 1 (PD-L1) status	(Ventana® PD-L1 SP142 IHC assay) in screening tumor tissue and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC1/2/3).
Exploratory Biomarker Objectives:	
• To assess biomarkers that are predictive of response to atezolizumab (i.e., predictive biomarkers), are associated with outcomes independent of treatment (i.e., prognostic biomarkers), as well as pharmacodynamic exploratory biomarkers in tumor tissue (e.g. screening, on-treatment*, and at disease progression sample*) and blood* and their association with disease status and/or response to study drug. • To assess changes in blood-* and tissue-based biomarkers during chemotherapy +/- atezolizumab treatment. • To assess whether immune biomarker findings from this study are consistent with findings in other studies in TNBC or in other tumor types.	• Relationship between tumor immune-related or disease type-related biomarkers (including but not limited to TILs and cluster of differentiation CD8) by immunohistochemistry in tumor 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 tumor tissues, and clinical outcomes. • Relationship between deoxyribonucleic acid (DNA) mutations and mutational burden assessed in tumor tissues, and clinical outcomes. • Relationship between exploratory biomarkers (including but not limited to circulating cell-free DNA, proteins and cytokines) in plasma* collected before treatment, during treatment and at disease progression, and clinical outcomes. • Changes in blood-* and tissue- based biomarkers under chemotherapy +/- atezolizumab treatment in relation to clinical outcome. • Correlation of immune biomarker findings in blood* and tissue samples from this study to findings from other studies in TNBC and other tumor types.

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

All requirements described in this protocol apply to the Global study, unless otherwise specified; requirements specific to the china sub-population are marked as such throughout the protocol.

STUDY DESIGN

DESCRIPTION OF STUDY

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

Global Study: A total of approximately 572 patients will be randomized in the study. Following the enrolment of 382 patients with inoperable recurrent TNBC (irrespective of programmed death-ligand 1 [PD-L1] tumor status, referred to as ‘all-comers’), approximately 190 additional patients with PD- L1-positive tumor status will be randomized, in order to reach approximately 330 patients with PD-L1-positive tumor status required for the primary endpoint analysis of overall survival (OS) in the PD-L1-positive population.

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

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

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

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

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

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

Allison et al. 2020). Triple-negative tumor status assessed locally prior to randomization requires subsequent confirmation (retrospectively) by the designated central laboratory.

A representative formalin-fixed, paraffin-embedded (ffpe) tumor specimen will be tested for pd-l1 expression, as assessed by central laboratory using the ventana (sp142) pd-l1 ihc assay. Tumor tissue should be of good quality based on total and viable tumor content and must be prospectively evaluated for pd-l1 expression prior to randomization. A tumor specimen obtained from relapsed metastatic or locally advanced disease may be submitted, if clinically feasible. If a fresh tumor sample is not clinically feasible, either the primary diagnosis, the surgical resection sample, or the most recent formalin-fixed, paraffin-embedded (ffpe) tumor biopsy should be used.

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

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

ARM A

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

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

  or

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

ARM B

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

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

  or

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

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

Patients who have been randomized will not be replaced.

Tumor assessments will be performed every 8 weeks (± 1 week) for the first 12 months after treatment initiation and every 12 weeks (± 1 week) thereafter until disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever

occurs first. Tumor assessments will be performed according to the specified schedule regardless of dose delays, interruptions, or discontinuations. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumor assessments according to the protocol-specified schedule until they experience disease progression, withdraw consent, or die, or until the study closes, whichever occurs first, even if they started another anti-cancer therapy after study treatment discontinuation.

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

Cross-over between treatment arms will not be allowed.

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

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

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

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

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

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

As described above, all patients enrolled in the Global study and all patients in the China sub- population will undergo mandatory tumor sample collection at screening. The mandatory tumor sample submitted prior to enrolment for ER/PR, HER2 and PD-L1 testing will be included in the exploratory biomarker evaluations. The schedule of sample collections for biomarker research is included in Appendix 2. Acceptable tumor samples for biomarker analyses are core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine needle aspirates,

brushings, cell pellets from pleural effusions, samples from bone metastases, and lavage samples are not acceptable.

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

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

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

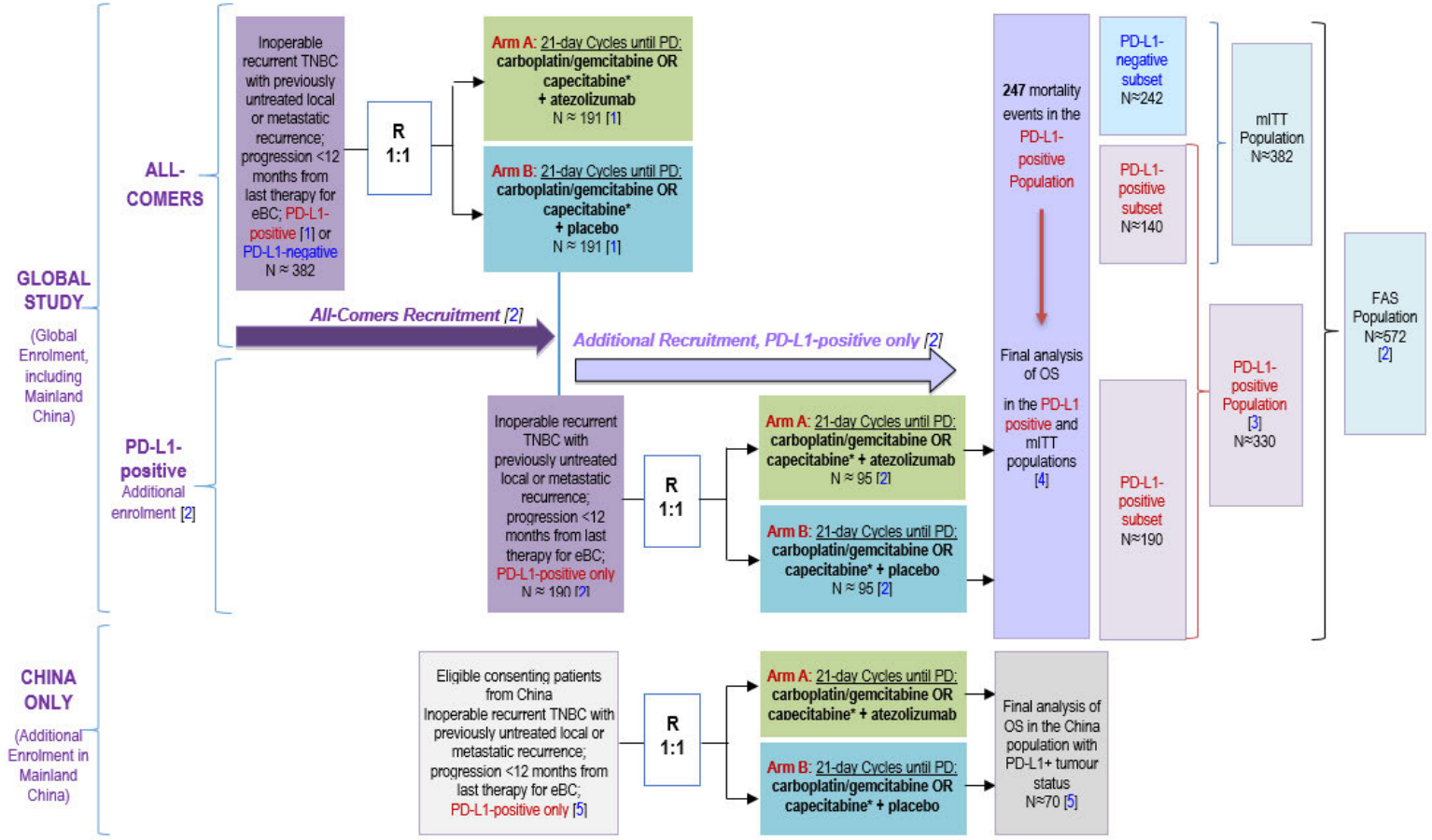
The schedule of sample collections for biomarker research is included in Appendix 2.

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

A Steering Committee (SC) will provide scientific oversight of the trial. Details of the composition and mandate of the SC will be provided in the SC Charter. In addition, an independent Data Monitoring Committee (iDMC) will be in place for periodic review of aggregate safety data during the study and an interim efficacy analysis, should the latter occur. Details of the composition of the iDMC, the safety review plan and procedures for interim analyses will be provided in the iDMC Charter.

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

Figure 1 Study Schema



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

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

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

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

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

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

Number of Patients

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

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

The study will be conducted at approximately 100 sites globally.

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

TARGET POPULATION

Inclusion Criteria

Patients must meet all the following criteria for study entry:

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

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

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

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

   China sub-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 randomization.
8. Measurable or non-measurable disease, as defined by RECIST 1.1 (Note: previously irradiated lesions may be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation).
9. Availability of a representative formalin-fixed paraffin-embedded (FFPE) tumor block (preferred) or at least 17 unstained slides obtained from relapsed metastatic or locally

advanced diseases may be submitted, if clinically feasible, with an associated pathology report, if available. If a fresh tumor sample is not clinically feasible, either the diagnosis sample, the primary surgical resection sample, or the most recent FFPE tumor biopsy sample should be used.

a. The tumor tissue should be of good quality based on total and viable tumor content and must be evaluated centrally for PD-L1 expression, as determined using Ventana (SP142) PD-L1 IHC assay prior to enrolment, with positivity defined as ≥1% of the tumor area occupied by PD-L1- expressing tumor-infiltrating immune cells of any intensity, and either locally or centrally for HER2, ER, and PR expression prior to enrolment. Patients whose tumor tissue is not evaluable for prospective central testing are not eligible.

b. If multiple tumor specimens are submitted, patients may be eligible if at least one specimen is evaluable and positive for PD-L1 expression (regardless whether the tissue is from an archival specimen or freshly collected relapsed disease).

   i. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) 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. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

10. Eastern Cooperative Oncology Group performance status 0-1.

11. Life expectancy ⩾ 12 weeks.

12. Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment administration (Cycle 1, Day 1):

    c. Absolute neutrophil count (ANC) ≥ 1500 cells/µL (without granulocyte colony stimulating factor [G-CSF] support within 2 weeks prior to the first study treatment administration). G-CSF may be administered until 2 weeks prior to Cycle 1, Day 1.

    d. Lymphocyte count ≥ 500/µL.

    e. Platelet count ≥ 100,000/µL (patients may be transfused to meet this criterion. Following transfusion, a 14-day period is required before Cycle 1, Day 1).

    f. Haemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion. Following transfusion, a 14-day period is required before Cycle 1, Day 1).

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

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

       v. Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 x ULN

    h. Serum bilirubin ≤ 1.5 x ULN

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

    i. Patients who are not receiving therapeutic anticoagulation: international normalised ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. Patients who are receiving an anticoagulant medicinal product must be on a stable anticoagulant regimen and have an INR which is not above the target therapeutic range during the 14 days preceding initiation of study treatment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Exclusion Criteria

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

Cancer-Specific Exclusion Criteria

20. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization

21. Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases.

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

a. Measurable or non-measurable disease, per RECIST v. 1.1, must be present outside the CNS

b. No history of intracranial haemorrhage or spinal cord haemorrhage

c. Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

d. There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.

e. The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 days prior to initiation of study treatment.

f. The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anticonvulsant therapy at a stable dose is permitted.

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

22. Symptomatic or rapid visceral progression

23. History of leptomeningeal disease

24. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) (patients with indwelling catheters such as PleurX® are allowed)

25. Uncontrolled tumour-related pain

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

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

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

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

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

27. Malignancies other than TNBC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%) and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localised prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)

General Medical Exclusion Criteria

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

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

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

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

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

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

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

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

Exclusion Criteria Related to Atezolizumab

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

Patients with the following are eligible:

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

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

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

History of radiation pneumonitis in the radiation field (fibrosis) is permitted

41. Active tuberculosis
42. Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that a live, attenuated vaccine will be required during atezolizumab/placebo treatment or within 5 months after the last dose of atezolizumab/placebo
43. Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway targeting agents
44. 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 randomization
45. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, mycophenolate, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, or anticipated requirement for systemic immunosuppressive medications during the trial, with the following exceptions:

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

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

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

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

48. Inability to swallow pills
49. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis
50. Known dihydropyrimidine dehydrogenase (DPD) deficiency or history of severe and unexpected reactions to fluoropyrimidine therapy in patients selected to receive capecitabine
51. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine in patients selected to receive capecitabine. Use of

these drugs is not allowed within 4 weeks of initiation of study treatment that includes capecitabine.

52. Hypersensitivity to any component of capecitabine drug formulation in patients selected to receive capecitabine.

Exclusion Criteria Related to Carboplatin/Gemcitabine

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

END OF STUDY AND LENGTH OF STUDY

The end of the study is defined (for the Global cohort and the China sub-population) as the last patient last visit (LPLV). The LPLV for the China sub-population may occur after the LPLV for the Global study.

Global Study

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

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

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

China sub-population

For patients randomized in China, the CCO date for the final OS analysis will be confirmed in the Statistical Analysis Plan (SAP) when the target number of mortality events have occurred in the PD-L1-positive population.

INVESTIGATIONAL MEDICINAL PRODUCTS

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

TEST PRODUCT (INVESTIGATIONAL DRUG)

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

COMPARATOR

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

CHEMOTHERAPY PARTNER

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

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

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

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

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

STATISTICAL METHODS

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

Consequently, the main analysis populations are defined as follows:

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

PRIMARY ANALYSIS

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

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

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

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

with patients grouped according to their treatment assigned at randomization.

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

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

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

The CCO date for the primary endpoint analysis will take place when the required number of 247 mortality events have been reported in the PD-L1-positive population. This is projected to

occur approximately 58 months after FPI. By this time-point, approximately 297 mortality events are expected to have occurred in the mITT population.

The final analysis of OS in the China sub-population will be conducted when sufficient OS events have occurred to demonstrate an acceptable probability of maintaining 50% of risk reduction compared with that estimated from the global population. Methods and exact timing for analysing data from the China sub-population will be provided in the SAP. Results from these analyses will be summarized in a separate report from the clinical study report (CSR) for the Global study.

DETERMINATION OF SAMPLE SIZE

Global Study

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

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

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

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

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

China sub-population:

After approximately 572 patients have been randomized in the Global study, global recruitment will be closed. Additional patients with PD-L1-positive tumour status may be subsequently randomized in China only, following the same randomization procedures and ratio (1:1), for a total enrolment of approximately 70 patients with PD-L1-positive tumour status in China (including patients from China enrolled in the Global cohort).

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

INTERIM ANALYSES

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

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

Appendix 2
Schedule of Assessments

Assessment Day (Window)	Screening	All Cycles		Treatment Discontinuation Visit*	Follow-Up Every 3 months (± 21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a1]	30 (±5) Days after Last Dose	
Written informed consent [b]	X				
Demographics and medical histories [c]	X				
HIV, HBV and HCV serology [d]	X				
Physical examination [e] [f]	X	x		x	
ECOG performance status [f]	X	x		x	
Vital signs [g]	X	x	x	x	
Weight	X	x		x	
Height	X				
12-lead electrocardiogram [h]	X	As clinically indicated			
Head CT or MRI	X				
Tumor assessments [i]	X	Until disease progression only: q8w for first 12 months, q12w thereafter			
EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L [j]		x		x	x [k]
FACT-G (GP5 only) [j]		Beginning at Cycle 2		x	x [k]
Haematology and serum chemistry [l] [f]	x [m]	x	x	x	
Coagulation panel (aPTT, INR) [a]	x [m]	x		x	
Urinalysis [n]	X	Cycle 3 and thereafter as clinically indicated		x	

Appendix 2
Schedule of Assessments (cont.)

Assessment Day (Window)	Screening	All Cycles		Treatment Discontinuation Visit*	Follow-Up Every 3 months (± 21 days)
	Days –28 to –1	Day 1 [a]	Day 8 [a1]	30 (±5) Days after Last Dose	
Pregnancy test [o] women of child-bearing potential only	x [m]	x		x	
TSH, free T3, free T4 [p]	X	Cycle 1 and every fourth cycle thereafter		x	
Mandatory FFPE tumor tissue sample [q] [r]	X				
Optional FFPE tumor tissue samples [s] [r]		Cycle 2 only		At disease progression	
Whole blood sample for germline DNA analysis [t] [r]		Cycle 1 only			
Mandatory plasma sample for biomarker analysis [r]		Cycles 1 - 3 only, then every 3 months		At disease progression	
ADA sample collection [u] [r]		Cycles 1 - 4 only		x	
Serum atezolizumab PK sample collections [r]		Cycles 1 - 4 only		x	
Concomitant medications [v]	X	x	x	x	
Adverse events [w]	X	x	x	x	x
Atezolizumab/placebo infusion [x]		x			
Carboplatin/gemcitabine administration [y] applicable patients only		x	x		
Capecitabine administration [z] applicable patients only		Days 1 to 14 only			
Survival and anti-cancer therapy follow-up [aa]					x

aPTT: activated partial thromboplastin time; ADA: anti-drug antibody; CT: computerised tomography; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L: EuroQoL 5 Dimension; ER/PR: oestrogen/progesterone receptors; FACT-G: Functional Assessment of Cancer Therapy: General; FFPE: fixed formalin paraffin embedded; HBV: hepatitis B virus; HCV: hepatitis C virus; HER2: human epidermal growth factor receptor 2; MRI: magnetic resonance imaging; PD-L1:programmed death ligand 1; PK: pharmacokinetics; q8w: every 8 weeks; q12w: every 12 weeks; QLQ-BR23: EORTC Breast Cancer-Specific Module; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone.

* The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

a. Assessments scheduled on the day of study treatment administration of each cycle should be performed prior to study treatment infusion unless otherwise noted. Assessments may be performed on Day 1 ± 3 days of each treatment cycle after cycle 1, unless otherwise noted (see footnote “f”, “j”, and Appendix 2). Coagulation panel tests on Day 1 of each cycle only apply to patients receiving capecitabine.

a1. Assessments on Day 8 (±1 day) of each cycle only apply to patients receiving carboplatin/gemcitabine. Patients receiving capecitabine treatment and patients who are no longer receiving carboplatin/gemcitabine treatment are not required to attend the Day 8 visit of each cycle.

b. Written informed consent is required before performing any study-specific screening test or procedure unless these have already been conducted as standard of care. Signing of the ICF can occur more than 28 days before initiation of study treatment. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to initiation of study treatment (except where otherwise specified) may be used for screening assessments rather than repeating such tests. Patients who do not meet the criteria for participation in this study may qualify for an additional re-screening opportunity (for a total of 2 screenings per patient) at the investigator's discretion, as described in Section 3.1.

c. Demographics include age, gender, self-reported race/ethnicity (where allowed by local regulations). Medical history includes reproductive status, smoking history, prior surgeries and cancer history (stage, date of diagnosis, prior anti-cancer treatment).

d. All patients will be tested for HIV locally prior to the inclusion into the study; HIV-positive patients will be excluded from the clinical study. Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) should be collected during screening and tested locally. Quantitative HBV DNA must be collected prior to randomization in patients who have negative serology for HBsAg and HBsAb and positive serology for HBcAb. See eligibility criteria for how to interpret HBV testing. All patients will be tested for HCV locally prior to inclusion into the study; Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

e. A complete physical examination must be conducted at screening and the treatment discontinuation visit. Symptom-driven physical examinations may be conducted during treatment and may be done ≤ 96 hours of Day 1 treatment, and as clinically indicated. Physical examinations will include a review of the main body organs and systems, with special attention to cardiovascular (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs), respiratory (e.g., shortness of breath, crackling), gastrointestinal (e.g., abdominal pain, digestive disorders) systems, and a neurological exam focusing on signs and symptoms potentially indicative of disorders such as myasthenia gravis, motor and sensory neuropathy, meningitis, and encephalitis.

f. ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

g. At all clinic visits where study treatment is administered, vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before and 30 (±10) minutes after each infusion (atezolizumab/placebo, as well as gemcitabine and carboplatin in applicable patients). Vital signs will also be determined every 15 (±5) minutes during the atezolizumab/placebo infusions if clinically indicated or if symptoms occurred during the previous

infusion. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

h. Standard 12-lead ECG, taken after resting in a supine position for at least 10 minutes. Additional cardiovascular monitoring (such as ECG and/or echocardiography) may be considered during the patient's study participation, if clinically indicated by the appearance of symptoms or findings at regular vital sign checks or medical examinations suggestive of cardiovascular disease (e.g. abnormally low or irregular pulse, chest pain, tachycardia, swollen legs, shortness of breath, crackling) especially if these cannot be explained by thyroid or electrolyte abnormalities.

i. Tumor assessments will be performed every 8 weeks for the first 12 months following randomization, and every 12 weeks thereafter, until PD, death, withdrawal of consent, or study termination by the Sponsor (whichever occurs first). All measurable and evaluable lesions should be assessed and documented at screening (baseline) and during the study in accordance with RECIST 1.1. Results must be reviewed by the investigator before dosing at the next cycle.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumor assessments according to the protocol-specified schedule until they experience disease progression, withdraw consent, or die, or until the study closes, whichever occurs first, even if they started another anti-cancer therapy after study treatment discontinuation.

j. EORTC QLQ-C30, QLQ-BR23, FACT-G (single item GP5 only), and EQ-5D-5L questionnaires must be completed by the patient at the investigational site, both during the treatment phase and follow-up period, at the start of the clinic visit (or within 3 days prior to the visit), before discussion of the patient's health state, lab results or health record, before administration of study treatment, and/or prior to the performance of any other study assessments that could bias patients' responses. Interview assessment by a member of the clinical staff will be allowed if the patient is not able to complete the measure on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. In case the treatment is delayed or omitted, the patient should repeat the PRO assessment at the next visit, corresponding to the treatment administration day.

k. Patients who complete or discontinue the study treatment phase for any reason will continue to complete the EORTC QLQ-C30, QLQ-BR23, FACT-G (single item GP5 only), and EQ-5D-5L questionnaires in-clinic during the follow-up period at the following timepoints: every 3 months (±21 days) for Year 1, every 6 months (± 21 days) for Years 2–3, and then annually (±21 days) thereafter.

l. Haematology consists of RBC count, haemoglobin, haematocrit, WBC count with differential (if clinically indicated), and platelet count. Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate (if part of standard analysis), calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Magnesium and phosphorus should be collected at screening, and thereafter only if clinically indicated. Glucose levels in diabetic patients receiving capecitabine must be monitored regularly during study treatment in accordance with local standards. Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms suggestive of pancreatitis.

m. Specified screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

n. Urinalysis by dipstick method includes specific gravity, pH, glucose, protein, ketones, and blood. During treatment, urinalysis will be performed on Day 1 of Cycle 3 and thereafter as clinically indicated.

o. Serum pregnancy test for women of childbearing potential at screening/baseline (within 14 days before Cycle 1, Day 1); after randomization, urine pregnancy tests will be performed at every cycle and at treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

p. TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter.

q. Results of PD-L1 testing of this mandatory screening tumor sample must be obtained from the designated central laboratory prior to enrolment. ER, PR, and HER2 triple-negative tumor status

may be assessed locally prior to screening according to the latest ASCO guidelines and confirmed retrospectively by the designated central laboratory. If a fresh tumor sample is not clinically feasible, either the diagnosis sample, the primary surgical resection sample, or the most recent FFPE tumor biopsy sample should be used. An FFPE block or at least 17 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Retrieval of archival tumor sample can occur outside the 28-day screening period. The sample will be included in exploratory biomarker research.

r. Refer to Appendix 2 for further details on sample collection times.

s. On-treatment and PD tumor samples for biomarker analyses are optional. They must be collected within 14 days prior to treatment on Day 1 of Cycle 2 and at disease progression (+/- 7 days) only if deemed clinically feasible by the investigator. Patients enrolled in China will not undergo optional tumor tissue collections (on-treatment or at disease progression).

t. Mandatory whole blood for germline DNA isolation will be collected during the Baseline visit (Cycle 1 Day 1). If this sample has not been collected during the Baseline visit, it can be collected at any of the following cycles. Patients enrolled in China will not undergo whole blood sample collection for germline DNA isolation.

u. Blood samples must be collected prior to study treatment administration on Day 1 of Cycles 1 to 4.

v. Includes all prescription or over-the-counter medications taken from 7 days prior to screening to the treatment discontinuation visit.

w. After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of atezolizumab/placebo or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, investigators should report any deaths, SAEs, or other AEs of concern that are considered related to prior treatment with the study drug. The investigator should follow each SAE and Grade ≥ 3 AE until the event has resolved to baseline grade, assessed as stable by the investigator, or until the patient withdraws consent or is lost to follow-up.

x. The first dosing day (Cycle 1 Day 1) should occur within 3 days from date of randomization. All subsequent atezolizumab/placebo infusions may be administered with a window of ±3 days. The first dose of atezolizumab/placebo will be delivered over 60 (±15) minutes; if the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

y. **Gemcitabine** will be administered as a 30-minute IV infusion at a dose of 1000 mg/m^2 on Day 1 and Day 8 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations. **Carboplatin** will be administered after the completion of gemcitabine administration by short-term IV infusion over 15 to 60 minutes at AUC 2 on Day 1 and Day 8 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations. The first dosing day (Cycle 1 Day 1) should occur within 3 days from date of randomization. All subsequent gemcitabine and carboplatin dosing on Day 1 may be administered within a window of ±3 days. Day 8 infusions of gemcitabine and carboplatin should not be administered any earlier than Day 7, but can be administered up to Day 11.

z. Patients should be instructed to take **capecitabine** 1000 mg/m^2 twice daily, approximately 12 hours apart orally on Days 1 to 14, followed by a 7-day rest period in each 3-week treatment cycle. In each cycle, the first dose of capecitabine should be taken in the evening of Day 1, and the last dose in the morning of Day 15. Patients should be instructed to return used and unused drug to the study site.

aa. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information until death, withdrawal of consent, loss to follow-up, or until study termination by the Sponsor. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits. Public information sources (e.g. county records) may also be used to obtain information about survival status only in case the patient withdrew from the study.

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity and Biomarker Samples

Global Study (Except Patients Enrolled in China):

Visit	Timepoint	Sample Type
Screening	Days -28 to -1	Mandatory FFPE tumor tissue sample [a]
During first line treatment		
Day 1, Cycle 1	Prior to first dose of any study treatment	Mandatory plasma sample for biomarker analysis
		Mandatory whole blood sample for germline DNA analysis [b]
Day 1 of Cycles 1 through 4	Prior to first dose of any study treatment	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)
Day 1, Cycles 1 and 3	30 ± 10 minutes after end of atezolizumab infusion	Atezolizumab PK (serum)
Day 1, Cycle 2	Prior to first dose of any study treatment	Optional FFPE tumor tissue sample [c]
		Mandatory plasma sample for biomarker analysis
Day 1, Cycle 3 and every 3 months thereafter	Prior to first dose of any study treatment	Mandatory plasma sample for biomarker analysis
Following discontinuation of study treatment		
At disease progression	NA	Optional FFPE tumor tissue sample [c]
		Mandatory plasma sample for biomarker analysis
Treatment Discontinuation Visit [d]	NA	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)

ADA = anti-drug antibody; NA = not applicable; PK = pharmacokinetics.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

a. Results of PD-L1 testing of this mandatory baseline tumor sample must be obtained from the designated central laboratory prior to enrolment. ER, PR, and HER2 triple-negative tumor status may be assessed locally prior to screening, and confirmed retrospectively by the designated central laboratory. If a fresh tumor sample is not available, the primary surgical resection sample or the most recent FFPE tumor biopsy sample may be used. The sample will be included in exploratory biomarker research. An FFPE block or at least 17 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

b. Mandatory whole blood for germline DNA isolation will be collected during the Baseline visit. If this sample has not been collected during the Baseline visit, it can be collected at any of the following cycles.

c. On-treatment tumor samples for biomarker analyses are optional. They must be collected within 14 days prior to treatment on Day 1 of Cycle 2 and at disease progression (±7 days) only if deemed clinically feasible by the investigator.

d. Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit 30 (±5) days after the last dose of study treatment.

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity and Biomarker Samples (cont.)

China sub-population:

Visit	Timepoint	Sample Type
Screening	Days -28 to -1	Mandatory FFPE tumor tissue sample [a]
During first line treatment		
Day 1 of Cycles 1 through 4	Prior to first dose of any study treatment	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)
Day 1, Cycles 1 and 3	30 ± 10 minutes after end of atezolizumab infusion	Atezolizumab PK (serum)
Following discontinuation of study treatment		
Treatment Discontinuation Visit [b]	NA	Atezolizumab PK (serum)
		Atezolizumab ADA (serum)

ADA = anti-drug antibody; NA = not applicable; PK = pharmacokinetics.

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

a. Results of PD-L1 testing of this mandatory baseline tumor sample must be obtained from the designated central laboratory prior to enrolment. ER, PR, and HER2 triple-negative tumor status may be assessed locally prior to screening, and confirmed retrospectively by the designated central laboratory. If a fresh tumor sample is not clinically feasible, the primary surgical resection sample or the most recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy may be used. An FFPE block or at least 17 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. The sample will be included in exploratory biomarker research upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC), and upon the review and approval by the Human Genetics Resources Administration of China (HGRAC) exploratory application.

b. Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit 30 (±5) days after the last dose of study treatment.

Note: Patients enrolled in China will not undergo the following sample collections:

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

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