

Official Title: A Phase III, Multicenter, Randomised, Double-Blind, Placebo-Controlled Study of Atezolizumab (Anti-Pd-L1 Antibody) in Combination With Paclitaxel Compared With Placebo With Paclitaxel for Patients With Previously Untreated Inoperable Locally Advanced or Metastatic Triple Negative Breast Cancer

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STATISTICAL ANALYSIS PLAN

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED INOPERABLE LOCALLY ADVANCED OR METASTATIC TRIPLE NEGATIVE BREAST CANCER

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Statistical Analysis Plan (SAP) MO39196, Version 3 has been amended to address U.S. FDA feedback (received on 22 November 2019) that patients enrolled in France should be included in the PD-L1–positive subpopulation of the hierarchical testing.

SAP MO39196, Version 4 therefore reverts to the contents of SAP MO39196, Version 2, albeit with modifications to Section 2.3 (Determination of Sample Size), where a typo was corrected. This correction does not affect the required number of events.

Additional minor revisions to improve clarity and correct errors and inconsistencies have also been implemented throughout.

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 cutoff date
C-DOR	duration of confirmed response
C-ORR	confirmed objective response rate
CR	complete response
CSR	Clinical Study Report
CV	coefficient of variation
DOR	duration of response
DRB	Data Review Board
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 questionnaire
FPI	first patient randomized
HR	hazard ratio
HRQoL	health-related quality of life
iDMC	independent Data Monitoring Committee
iDCC	independent Data Coordinating Center
IRBs/ECs	Institutional Review Boards/Ethics Committees
ITT	intent to treat
IxRS	Interactive voice/web response system
LS Mean	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPT	non-protocol therapy
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PFS2	second-line PFS
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PT	preferred term
RECIST	Response Evaluation Criteria in Solid
RPFST	Tumors rank-preserving structural failure
SAE	time serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TTD	time to 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 MO39196 (IMpassion131).

2. **STUDY DESIGN**

2.1 **PROTOCOL SYNOPSIS**

The Protocol Synopsis is in [Appendix 1](#) and the study schema in [Appendix 2](#). For additional details, see the Schedule of Assessments in [Appendix 3](#) and [Appendix 4](#).

2.2 **OUTCOME MEASURES**

See the Protocol Synopsis in [Appendix 1](#) for a description of the outcome measures.

2.3 **DETERMINATION OF SAMPLE SIZE**

2.3.1 **Global Study**

The purpose of this event-driven study is to evaluate the efficacy of TECENTRIQ® (atezolizumab) plus paclitaxel compared to placebo plus paclitaxel as measured by progression-free survival (PFS) (either investigator-assessed disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] or death from any cause, whichever occurs first).

PFS will be assessed hierarchically in the following fixed order: (1) PFS in the programmed death–ligand 1 (PD-L1)–positive subpopulation followed by (2) PFS in the intent-to-treat (ITT) population.

The sample size for the global study was determined based on the following assumptions:

- Median PFS of 5.0 months in patients with PD-L1–positive tumor status randomized to the placebo plus paclitaxel group (as detected in patients with PD-L1–positive triple-negative breast cancer [TNBC] in the placebo plus albumin-bound (nab-paclitaxel control arm of IMpassion130) ([Schmid et al. 2018](#)))
- Treatment effect (between-group difference) of approximately 3 months in the median PFS (hazard ration [HR] 0.62) in the PD-L1–positive subpopulation (HR as detected in the PD-L1–positive subpopulation of IMpassion130) ([Schmid et al. 2018](#)))
- Randomization ratio of 2:1
- Approximately 40% of the enrolled patients are expected to have PD-L1–positive tumor status (as detected in IMpassion130) ([Schmid et al. 2018](#)))
- 80% power and an overall 2-sided α of 0.05
- Drop-out rate of 10%

Based on these assumptions and parameters, approximately 213 evaluable patients with PD-L1–positive tumor status (approximately 142 in the atezolizumab plus paclitaxel

group and approximately 71 in the placebo plus paclitaxel group) and a total of 155 PFS events are required to detect a between-group difference of approximately 3 months in the final analysis of median PFS (HR 0.62). Assuming that approximately 40% of the enrolled patients will have PD-L1–positive tumor status, and to account for an estimated drop-out rate of 10%, approximately 600 patients will be randomized into the global study (approximately 400 in the atezolizumab plus paclitaxel group and approximately 200 in the placebo plus paclitaxel group). Anticipating a global recruitment period of approximately 23 months (up to 40 patients per month), the clinical cutoff date (CCOD) for the primary (final) PFS analysis in the subpopulation with PD-L1–positive tumor status is expected to occur approximately 29 months after the first patient randomized (FPI) into the global study.

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

Operating characteristics (power and expected total number of events) for HR values for median PFS and median OS in PD-L1–positive subpopulation are provided in [Table 1](#).

Table 1 Operating Characteristics for the Global Study

	Total	Atezo+P	PI+P	Treatment Δ	HR	Power	Duration of Study
mPFS, PD-L1–positive subpopulation (primary)	—	8 mos	5.0 mos	3 mos	0.62	80%	29 mos
Total events	155	—	—	—	—	—	—
Evaluable patients	~213	~142	~71	—	—	—	—
mPFS, ITT population (primary)	—	—	—	—	—	—	—
Total events	~395	—	—	—	—	—	—
Evaluable patients	~540	~360	~180	—	—	—	—
Total patients	~600	~400	~200	—	—	—	—
mOS, PD-L1–positive subpopulation (secondary)	—	25.0 mos	15.5 mos	9.5 mos	0.62	~70%	40 mos
Total events	122	—	—	—	—	—	—

atezo=atezolizumab; HR=hazard ratio; m=median; mos=months; P=paclitaxel; PFS=progression-free survival; PI=placebo; OS=overall survival.

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

2.3.2 Controlling for Type I Error

All tests will be performed at a two-sided α 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:

1. PFS by RECIST v1.1 (PD-L1–positive subpopulation, as defined in Section 4.1)
2. PFS by RECIST v1.1 (ITT population)
3. OS (PD-L1–positive subpopulation, as defined in Section 4.1)
4. OS (ITT population)
5. Objective response rate (ORR) by RECIST v1.1 (PD-L1–positive response-evaluable population, as defined in Section 4.1).
6. ORR by RECIST v1.1 (response-evaluable population)

The primary analysis population is considered to be the PD-L1–positive subpopulation. If PFS is found to be significant for this population, PFS will be tested in the ITT population.

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

The remaining secondary endpoints (12-month and 18-month OS rates, time to deterioration [TTD], PFS rate at 12 months, duration of response [DOR], and clinical benefit rate [CBR], as well as confirmed objective response rate [C-ORR] and duration of confirmed response [C-DOR]) will not be adjusted for multiple testing.

2.3.3 China Population

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

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

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

2.4 ANALYSIS TIMING

The CCOD date for the primary (final) analysis of PFS will take place when the required number of 155 PFS events have been observed in the PD-L1–positive subpopulation. PFS in the ITT population will also be analyzed at this time.

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

For OS, a group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate ([Lan and DeMets 1983](#)).

The information fraction at the time of each analysis will be re-calculated using the actual number of events included in the analysis, and the nominal alpha level re-calculated accordingly. Testing on OS will be conducted hierarchically only if the null hypotheses for the ITT and PD-L1–positive populations in the testing of PFS have been rejected.

Table 2 Timing of PFS and OS Analyses in the PD-L1–Positive Subpopulation

Analysis	Timing of Analysis	Percent Information	Nominal Two-Sided Alpha Level	Cumulative Two-Sided Alpha Level	Power (%)
PFS primary analysis	155 PFS events ^a	100%		0.05	80%
OS interim analysis	~83 OS events ^a	67%	0.012	0.012	
OS final analysis	122 OS events ^a	100%	0.046	0.05	~70%
China analysis	i) 36 PFS events ii) at the global primary PFS analysis if occurring before (i)	i) 100% ii) as observed at the time of primary PFS analysis for global population	—	—	—

PFS=progression-free survival; OS=overall survival.

^a Number of outcome events in the PD-L1–positive subpopulation

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization to atezolizumab plus paclitaxel or placebo plus paclitaxel will occur in a 2:1 ratio using a permuted-block randomization method. The randomization will be stratified on the following factors:

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

3.2 INDEPENDENT REVIEW FACILITY

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints by an Independent Review Committee (e.g., to meet potential requests by a reviewing health authority).

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 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:

- ITT population: All randomized patients, whether or not the assigned study treatment was received
- PD-L1–positive subpopulation: Patients in the ITT population whose PD-L1 status was IC1/2/3 at the time of randomization
- Response-evaluable population: Patients in the ITT population with measurable disease at baseline
- PD-L1–positive response-evaluable population: Patients in the PD-L1–positive subpopulation with measurable disease at baseline
- DOR-evaluable population: Patients in the ITT population with measurable disease at baseline and an objective response
- C-DOR-evaluable population: Patients in the ITT population with measurable disease at baseline and a confirmed objective response
- Patient reported outcome (PRO)–evaluable population: Patients in the ITT population with baseline PRO assessment and at least one post-baseline PRO assessment in the questionnaire of interest (European Organization for the

Research and Treatment of Cancer [EORTC] Quality-of-Life Questionnaire [QLQ] C30, EORTC QLQ BR-23 or FACT-G).

- Safety-evaluable population: Patients who received any amount of any study drug
- Pharmacokinetic (PK)-evaluable population: All 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.

A subset of analyses of efficacy and safety will be conducted in the China population, defined as all patients enrolled in China (either in the global study or in the additional enrollment).

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, patient disposition, reason for discontinuation from study treatment, and reason for study termination will be summarized for all patients in the ITT population.

Major protocol deviations, including violations of inclusion/exclusion criteria and deviations during study conduct, will be reported and summarized.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The following analyses will be based on the ITT population.

Demographic variables such as age, sex, race/ethnicity, stratification variables, and other relevant baseline characteristics will be summarized using means, 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 and will be data reported on Cycle 2, Day 1 for the FACT-G questionnaire.

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

Prior cancer therapy, prior cancer radiotherapy, prior cancer surgery, follow-up cancer therapy, anti-cancer therapies administered after progression, anti-cancer therapies administered before progression or for patients with no progression, follow-up cancer radiotherapy, on-study radiotherapy, on-study and follow-up cancer-related medical/surgical procedures 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. Therapies will be reviewed by the Medical Monitor on an ongoing basis and revised if necessary.

4.4 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be performed for the PD-L1-positive subpopulation and the ITT population, unless specified otherwise.

Hypothesis tests will be two-sided unless otherwise indicated. The overall type I error (α) for this study is 0.05.

4.4.1 Primary Efficacy Endpoint

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 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-positive subpopulation followed by
2. PFS in the ITT population.

The following analyses will be performed:

- Treatment comparisons will be based on the stratified log-rank test. The stratification factors will be three of the four pre-defined randomization stratification factors: tumor PD-L1 status (IC0 vs. IC1/2/3), prior taxane treatment (yes vs. no), and presence of liver metastases (yes vs. no) and will be obtained from the interactive Web/phone response system (IxRS). 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 will be provided. Results from an unstratified analysis will also be provided.
- Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm ([Brookmeyer and Crowley 1982](#)).

4.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in this study are:

- OS assessed in the PD-L1–positive subpopulation and in the ITT population
- ORR by investigator assessment using RECIST v1.1, assessed in the PD-L1–positive response-evaluable population and the response-evaluable population
- 12-month, 18-month, and 24-month OS rates in the PD-L1–positive subpopulation and the ITT population
- TTD in Global Health Status/HRQoL (Items 29 and 30 of the EORTC QLQ-C30), in the PRO-evaluable population
- PFS rate at 12 months in the PD-L1–positive subpopulation and the ITT population
- DoR by investigator assessment using RECIST v1.1 in the DOR-evaluable population
- Clinical benefit rate (CBR) by investigator assessment using RECIST v1.1 in the response-evaluable population,
- C-ORR, by investigator assessment using RECIST v1.1, assessed in the PD-L1–positive response-evaluable population and the response-evaluable population
- C-DOR by investigator assessment using RECIST v1.1, assessed in the C-DoR–evaluable population

All tests will be performed at an overall 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:

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

The remaining secondary endpoints (12-month, 18-month, and 24-month OS rates, TTD, PFS rate at 12 months, DOR, CBR, as well as C-ORR and C-DOR) will not be adjusted for multiple testing.

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

4.4.2.1 Secondary Endpoint: Overall Survival

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.

OS will be assessed hierarchically in the PD-L1–positive subpopulation and in the ITT population in a similar manner as for PFS.

An interim analysis of OS will be performed at the time of the primary (final) analysis of PFS. A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate for the OS analyses ([Lan and DeMets 1983](#)).

The final analysis of OS will take place when the required number of 122 mortality events have been observed in the PD-L1–positive subpopulation.

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

4.4.2.2 Overall Survival Rate at 12, 18, and 24 Months

OS rate at 12, 18 and 24 months will be estimated for each treatment arm using Kaplan-Meier methodology, along with 95% CI calculated with the standard error derived from the Greenwood formula.

4.4.2.3 Time to Deterioration in Global Health Status

Time to deterioration (TTD) in Global Health Status (GHS)/HRQoL will be analyzed based on the EORTC QLQ-C30 in the PRO-evaluable population and among the PD-L1–positive patients within the PRO-evaluable population.

Deterioration in GHS/HRQoL (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/HRQoL 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.

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

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

4.4.2.4 PFS Rate at 12 Months

The PFS rate at 12 months will be estimated for each treatment arm using Kaplan-Meier methodology, along with 95% CI calculated with the standard error derived from the Greenwood formula.

4.4.2.5 Best Overall Response

The best overall response (BOR) for a patient is defined as the most favorable outcome, according to 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 and the PD-L1–positive response-evaluable population and will be summarized by treatment arm.

4.4.2.6 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 and the PD-L1–positive response-evaluable 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 PFS. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution. 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 be analyzed for U.S. registrational purposes. Confirmation of response was not required in this study; therefore, a confirmatory scan after 4 weeks as recommended in the RECIST guideline Version 1.1 (Eisenhauer 2009) was not planned. Confirmed response will be calculated using the next scheduled scan (after 8 weeks for the first 12 months following randomization and after 12 weeks thereafter). It is acknowledged that this will 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 and the PD-L1–positive response-evaluable population. Similar analyses as for ORR will be performed.

4.4.2.7 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 per RECIST v1.1 or death from any cause, whichever occurs first. DOR will be analyzed in the DOR-evaluable population and among the PD-L1–positive patients in the DOR-evaluable 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 PFS will be used for the analysis of DOR except that the analysis will not be stratified.

Similar to C-ORR, C-DOR will be analyzed for U.S. registrational purposes. Confirmed response will be calculated using the next scheduled 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 and among the PD-L1–positive patients in the C-DOR–evaluable population. Similar analyses as for DOR will be performed.

4.4.2.8 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.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 Second-Line PFS (PFS2)

Second-line PFS (PFS2) is defined as time from randomization to tumor progression or death from any cause on next line of treatment, whichever occurs first. Patients who are alive and who have not experienced disease progression on the next line of treatment at the time of the CCOD will be censored at the last date known to be alive.

PFS2 will be compared between treatment arms in the subset of patients receiving second-line treatment using similar methods as for the primary endpoint of PFS.

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

EORTC data will be analyzed based on the PRO-evaluable population for EORTC QLQ-C30 and EORTC BR23, unless specified otherwise.

Summary statistics (mean, standard deviation, 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 TTD 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-event analysis to investigate the time to clinically meaningful deterioration in the functional (physical, role, and cognitive) subscales of the EORTC QLQ-C30 will be conducted to assess the time from baseline to worsening in patient function.

Deterioration in function will be assessed using the published corresponding MIDs ([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 subscale EORTC QLQ-C30 data are available if baseline and post-baseline subscale EORTC QLQ-C30 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 (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 standard error (SE) will also be calculated for each LS Mean.

The EORTC QLQ-C30 and QLQ-BR23 data will be scored according to the EORTC scoring manual (Fayers 2001). 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, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for the ITT population and for the PD-L1–positive patients.

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.

4.4.3.4 Burden of Treatment—FACT-G Single Item GP5 Data

The burden of treatment associated with the addition of atezolizumab to paclitaxel will be measured by the GP5 item ("I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G quality-of-life instrument (Cella et al. 1993). GP5 item scores will be derived from a 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 absolute scores, change from baseline scores, and the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported for item GP5 ("I am bothered by side effects of treatment") from the FACT-G physical wellbeing subscale using the FACT-G–evaluable population and the PD-L1–positive patients within the FACT-G–evaluable population.

4.4.4 Sensitivity Analyses

4.4.4.1 Sensitivity Analyses of Progression-Free Survival Mistratification

The primary analysis on PFS will be repeated by using the stratification factors based on the eCRF as a sensitivity analysis.

Missing Tumor Assessment

The impact of missing scheduled tumor assessments on the primary endpoint of 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 the primary endpoint of investigator-assessed 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.

Progression-Free Survival by IRC

An analysis of PFS on the basis of IRC assessments will be performed after centralized, independent review of response endpoints by the IRC using the same analyses as specified for PFS on the basis of investigator assessment.

4.4.4.2 Sensitivity Analyses of Overall Survival Mistratification

The analysis on OS will be repeated by using the stratification factors based on the eCRF as sensitivity analyses.

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. 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). Censoring for treatment switching will be applied to OS, analogous to censoring for NPT for PFS (see Section 4.4.4.1).

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.

4.4.4.3 Sensitivity Analyses of Objective Response Rate ORR by IRC

An analysis of ORR on the basis of the IRC assessments will be performed after centralized, independent review of response endpoints by the IRC using the same methodology as specified for ORR on the basis of investigator assessment. Measurable disease at baseline will be determined by the assessment by the IRC.

4.4.4.4 Sensitivity Analyses of Duration of Response DOR by IRC

An analysis of DOR on the basis of the IRC assessments will be performed after centralized, independent review of response endpoints by the IRC using the same methodology as specified for DOR on the basis of investigator assessment. Objective response will be determined by the assessment by the IRC.

4.4.5 Subgroup Analyses

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

- PD-L1 status
- Baseline characteristics: age group, race, geographical regions (per IxRS), baseline ECOG performance status, prior taxane treatment (per eCRF), presence of liver metastases (per eCRF)
- Disease involvement: brain metastases, nodal disease only, bone metastases, baseline disease status, number of sites
- Disease history: prior anthracycline treatment, prior therapy, time from last surgery until diagnosis with metastatic or locally advanced unresectable disease, median time from initial diagnosis until local recurrence or metastatic disease

Summaries of PFS and OS, 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. If applicable, random effects models might be used to further explore potential region/center effects.

Subgroups analysis for ORR will also be performed by PD-L1 status. 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.

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.

Sparse plasma paclitaxel concentrations data will be summarized with use of descriptive statistics as stated above.

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, unless specified otherwise.

4.6.1 Exposure of Study Medication

Study treatment (atezolizumab/placebo and paclitaxel) 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 adverse events occur, the maximum severity reported will be used in the summaries. Only adverse events occurring on or after the first dose of any study treatment will be included in the summary tables of adverse events. Adverse events occurring prior the first dose of any study treatment will be summarized separately as “baseline signs and symptoms.”

The following AEs will be summarized as relevant:

- AEs
- AEs by i) highest NCI CTCAE grade, ii) highest NCI CTCAE grade grouped by Grades 1–2,3–4,5
- AEs with a difference of at least 5% between treatment arms
- Serious adverse events (SAEs)
- SAEs with an incidence rate of at least 1%
- SAEs by highest NCI CTCAE grade

- SAEs related to i) any study treatment, ii) atezolizumab/placebo, iii) paclitaxel
- Grade 3–4 AEs
- Grade 3–4 AEs with an incidence rate of at least 2%
- Grade 3–4 AEs with a difference of at least 2% between treatment arms
- Grade 3–5 AEs with a difference of at least 2% between treatment arms
- AEs leading to discontinuation of i) any study treatment, ii) atezolizumab/placebo, iii) paclitaxel
- AEs leading to dose reduction or interruption of i) any study treatment, ii) atezolizumab/placebo, iii) paclitaxel
- AEs leading to dose reduction or interruption of any study treatment with an incidence rate of at least 1%
- AEs resulting in death
- AEs related to i) any study treatment, ii) atezolizumab/placebo, iii) paclitaxel

Adverse events of special interest (AESI) will be evaluated as follows:

- All 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 by i) highest NCI CTCAE grade, ii) highest NCI CTCAE grade grouped by Grades 1–2,3–4,5
- AESIs leading to atezolizumab/placebo discontinuation by highest NCI CTCAE grade
- AESIs leading to atezolizumab/placebo interruption by highest NCI CTCAE grade
- Serious AESIs
- Serious AESIs by highest NCI CTCAE grade
- AESIs leading to discontinuation of i) any study treatment, ii) atezolizumab/placebo
- AESIs leading to dose reduction or interruption of i) any study treatment, ii) atezolizumab/placebo
- AESIs requiring use of corticosteroids (previously named Immune-mediated adverse events)
- AESIs requiring use of corticosteroid leading to discontinuation of i) any study treatment, ii) atezolizumab/placebo, iii) paclitaxel
- AESIs requiring use of corticosteroid leading to dose reduction or interruption of i) any study treatment, ii) atezolizumab/placebo, iii) paclitaxel
- Serious AESIs requiring use of corticosteroid

- AEs requiring use of corticosteroids by i) highest NCI CTCAE grade, ii) highest NCI CTCAE grade grouped by Grades 1–2,3–4,5

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

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, 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 paclitaxel) according to prospectively determined PD-L1 expression, analyses of the relationship between PD-L1 status by immunohistochemistry (PD-L1 positive IC1/2/3 vs. PD-L1 negative IC0) in recently (within 3 months prior to randomization) obtained or, if clinically not feasible, archival primary tumor tissues and clinical efficacy and safety outcomes will be undertaken.

4.7.1 Exploratory Biomarker Analyses

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

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

- Relationship between tumor immune-related or disease type-related biomarkers (including but not limited to TILs and 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 RNA expression analysis in tumor tissues and clinical outcomes.
- Relationship between DNA mutations and mutational burden by NGS genotyping in tumor tissues
- Relationship between exploratory biomarkers (including but not limited to circulating cell-free DNA, proteins and cytokines) in plasma collected before treatment, during treatment, and at disease progression and clinical outcomes.
- Changes in blood- and tissue-based biomarkers under paclitaxel +/- atezolizumab treatment
- In addition, correlation of immune biomarker findings in blood and tissue samples from this study to findings from other studies in TNBC and other tumor types will be evaluated.

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

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

There will be one interim analysis of OS (in the PD-L1–positive subpopulation and the ITT population) at the time of the primary (final) analysis of PFS. The final analysis of OS will be performed after 122 deaths have been observed in the PD-L1–positive subpopulation. A group sequential design (Lan-DeMets with O’Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets 1983). Testing on OS will be conducted hierarchically only if the null hypothesis for testing on PFS (in the PD-L1–positive subpopulation and the ITT population) has been rejected.

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

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. 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 Jul;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.
- DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med* 1994;13:1341- 52; discussion 1353-6.
- 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.
- Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika.* 1983;70:659–663.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- 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.
- Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast Cancer. *N Engl J Med.* 2018.
- 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

PROTOCOL SYNOPSIS

TITLE: A PHASE III, MULTICENTER, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH PACLITAXEL COMPARED WITH PLACEBO WITH PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED INOPERABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER

PROTOCOL NUMBER: MO39196

VERSION NUMBER: 6.0

EUDRACT NUMBER: 2016-004024-29

IND NUMBER: 123277

NCT NUMBER: NCT03125902

TEST PRODUCT: Atezolizumab (MPDL3280A)

PHASE: Phase III

INDICATION: Triple-negative breast cancer (TNBC)

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of atezolizumab plus paclitaxel compared with placebo plus paclitaxel in patients with inoperable locally advanced or metastatic triple-negative breast cancer (TNBC) who have not received prior systemic therapy for these conditions. Specific objectives and corresponding endpoints for the study are outlined in Table 1 below.

Table 1 Study Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by progression-free survival (PFS) 	<ul style="list-style-type: none"> PFS, defined as the time from randomisation to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause during the study, whichever occurs first. PFS will be tested hierarchically in the following fixed order: <ul style="list-style-type: none"> In the subpopulation with programmed death-ligand 1 (PD-L1)-positive tumour status. In the intent-to-treat (ITT) population.

Secondary Efficacy Objectives:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by overall survival (OS), 12-month and 18-month OS rates, health-related quality of life (HRQoL), 12-month PFS rate, objective response rate (ORR), duration of objective response (DoR), and clinical benefit rate (CBR) 	<ul style="list-style-type: none"> OS, defined as the time from randomisation to death from any cause in the PD-L1-positive subpopulation. OS in the ITT population. 12-month and 18-month OS rates. Time to deterioration (TTD) in Global Health Status/HRQoL, defined by a minimally important decrease of ≥ 10 points on the Global Health Status /HRQoL scale (items 29 and 30) of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). PFS rate at 12 months. ORR, defined as the percentage of patients with measurable disease at baseline, who have achieved complete response (CR) or partial response (PR), as determined by the investigator using RECIST v1.1. DoR, defined as the period from the date of initial CR or PR until the date of PD or death from any cause during the study, whichever occurs first. DoR is evaluated in the subset of patients with measurable disease at baseline, who have achieved an objective response. CBR, defined as the percentage of patients who have achieved CR, PR, or stable disease (SD) that lasts at least 6 months. <p>In addition, as per FDA request, confirmed objective response rate (C-ORR) and duration of confirmed response (C-DoR) will be analysed. Details will be provided in the Statistical Analysis Plan (SAP).</p>
Exploratory Efficacy Objectives:	
<ul style="list-style-type: none"> To evaluate the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by second line PFS (PFS2) 	<ul style="list-style-type: none"> PFS2, defined as time from randomisation to tumour progression or death from any cause on next line of treatment, whichever occurs first.
<ul style="list-style-type: none"> To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab plus paclitaxel compared with placebo plus paclitaxel, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23), using descriptive statistics 	<ul style="list-style-type: none"> Changes from baseline score in patient function (physical, role, social, emotional, cognitive) and disease/treatment-related symptoms by cycle, and between treatment arms as assessed by all function scales and symptom items/scales of the EORTC QLQ-C30 and QLQ-BR23.
<ul style="list-style-type: none"> To evaluate PROs of Global Health Status/HRQoL scale associated with atezolizumab plus paclitaxel compared with placebo plus paclitaxel, as measured by the Global Health Status/HRQoL scale of the EORTC QLQ-C30, using descriptive statistics 	<ul style="list-style-type: none"> Changes from baseline score in HRQoL by cycle, and between treatment arms as assessed by the Global Health Status/HRQoL scale (items 29 and 30) of the EORTC QLQ-C30.

Exploratory Efficacy Objectives (cont.):	
<ul style="list-style-type: none"> To evaluate and compare between treatment arms patient's health utility as measured by the European Quality of Life 5 Dimension (EQ-5D) questionnaire to generate utility scores for use in economic models for reimbursement 	<ul style="list-style-type: none"> Health utility scores of the EQ-5D-5L (5-level version) questionnaire. European Quality of Life Visual Analogue Scale (EQ-VAS).
<ul style="list-style-type: none"> To evaluate the burden of treatment associated with the addition of atezolizumab to paclitaxel, as measured by the GP5 item from the physical wellbeing subscale of the Functional Assessment of Cancer Therapy – General (FACT-G) quality of life instrument. 	<ul style="list-style-type: none"> Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G
Specific Efficacy Objectives for patients recruited in China [1]:	
<ul style="list-style-type: none"> The objective of the China population analyses is to evaluate whether the efficacy of atezolizumab plus paclitaxel compared with placebo plus paclitaxel as measured by PFS in the China population (enrolled in the Global study and during additional recruitment in China) is consistent with the efficacy observed in the Global population (Global study). 	<ul style="list-style-type: none"> As described for the Global study.
Pharmacokinetic Objective:	
<ul style="list-style-type: none"> To characterise the PK of atezolizumab when administered concomitantly with paclitaxel To characterise the PK of paclitaxel when administered concomitantly with atezolizumab 	<ul style="list-style-type: none"> Serum concentration (C_{min} and C_{max}) of atezolizumab at specified timepoints Plasma concentration (C_{min} and C_{max}) of paclitaxel at specified timepoints
Safety Objective:	
<ul style="list-style-type: none"> To evaluate the safety of atezolizumab plus paclitaxel compared with placebo plus paclitaxel 	<ul style="list-style-type: none"> Incidence of adverse events (AEs), with severity determined through use of the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) Change from baseline in targeted vital signs and physical findings Change from baseline in targeted clinical laboratory test results

Immunogenicity Objective:	
<ul style="list-style-type: none"> To evaluate the immunogenicity of atezolizumab 	<ul style="list-style-type: none"> Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline. For patients who show evidence of immune-mediated toxicity, samples will be collected and tested for anti-nuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA), circulating anti-neutrophil cytoplasmic antibody (s-ANCA), and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA).
Exploratory Immunogenicity Objective:	
<ul style="list-style-type: none"> To evaluate potential effects of ADAs 	<ul style="list-style-type: none"> Relationship between ADA status and efficacy, safety, or PK endpoints.
Biomarker Objective:	
<ul style="list-style-type: none"> To assess the activity and safety of atezolizumab according to PD-L1 status 	<ul style="list-style-type: none"> Relationship between PD-L1 protein expression by immunohistochemistry (Ventana® SP142 assay) in tumour tissues obtained within 3 months prior to patient randomisation [2], and clinical outcomes (predefined analysis according to PD-L1 stratification groups, i.e., IC0 versus IC 1/2/3).
Exploratory Biomarker Objectives:	
<ul style="list-style-type: none"> To assess biomarkers that are predictive of response to atezolizumab (i.e., predictive biomarkers), are associated with outcomes independent of treatment (i.e., prognostic biomarkers), as well as pharmacodynamic exploratory biomarkers in tumour tissues (obtained at baseline/within 3 months prior to randomisation [2], on-treatment, and at disease progression) and blood and their association with disease status and/or response to study drug. To assess changes in blood- and tissue-based biomarkers during paclitaxel +/- atezolizumab treatment. To assess whether immune biomarker findings from this study are consistent with findings in other studies in TNBC or in other tumour types 	<ul style="list-style-type: none"> Relationship between tumour immune-related or disease type-related biomarkers (including but not limited to TILs and cluster of differentiation [CD]8) by immunohistochemistry in tumour tissues, and clinical outcomes. Relationship between PD-L1 status measured by various immunohistochemistry assays and clinical outcomes. Relationship between certain molecular subgroups and pre-defined gene signatures by ribonucleic acid (RNA) expression analysis in tumour tissues, and clinical outcomes. Relationship between deoxyribonucleic acid (DNA) mutations and mutational burden by NGS genotyping in tumour tissues. Relationship between exploratory biomarkers (including but not limited to circulating cell-free DNA, proteins and cytokines) in plasma collected before treatment, during treatment and at disease progression, and clinical outcomes. Changes in blood- and tissue- based biomarkers under paclitaxel +/- atezolizumab treatment. Correlation of immune biomarker findings in blood and tissue samples from this study to findings from other studies in TNBC and other tumour types.

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

[2] If a tumour sample taken within 3 months before randomisation is not available and a tumour biopsy is not clinically feasible, the primary surgical resection sample or the most recent FFPE tumour biopsy sample may be used. Of these additional options, the most recent sample should be used.

Study Design

Description of the Study

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

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

- **Global study:** Approximately 600 patients are planned to be randomised at approximately 200 sites globally (in select countries from Europe, Asia/Pacific, as well as North-, and South America). Patients will be randomised centrally, using an interactive voice or web response system (IxRS), in a 2:1 randomisation ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle, plus paclitaxel (90 mg/m²) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Randomisation will be stratified by the following factors: tumour PD-L1 status (PD-L1 expression on tumour-infiltrating immune cells [ICs] assessed by immunohistochemistry [IHC]) (IC0 vs. IC1/2/3), prior taxane treatment (yes vs. no), presence of liver metastases (yes vs. no), and region (North America vs. Western Europe/Australia; vs. Eastern Europe/Asia Pacific vs. South America). Randomised patients will not be replaced.
- **Additional enrolment in China:** After approximately 600 patients have been randomised in the Global study, global recruitment will be closed. Additional patients may be subsequently randomised in China only, following the same randomisation procedures and ratio (2:1), to ensure a total enrolment of approximately 130 patients in mainland China (including patients enrolled in the Global study), referred to as the China Population. The schedule of assessments and study treatments for these patients will be identical to those in the Global study. Analyses based on the China Population will be performed and summarised separately.

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

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

Tumour assessments will be performed at screening/baseline, approximately every 8 weeks (± 1 week) for the first 12 months after randomisation, and every 12 weeks thereafter until disease progression (PD), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Tumour assessments performed as part of standard of care prior to obtaining informed consent and within 28 days of Cycle 1,

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

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

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

The study Steering Committee (SC) will provide scientific oversight for the trial. Details on the composition and mandate of the SC will be provided in the SC Charter. In addition, an independent Data Monitoring Committee (iDMC) will be in place for periodic review of aggregate safety data. Details on the composition of the iDMC and safety review plan will be provided in the iDMC Charter.

Number of Patients

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

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

China enrolled in the Global study).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

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

Prior radiation therapy for metastatic disease is permitted. There is no required minimum washout period for radiation therapy; however, patients should have recovered from the effects of radiation before randomisation.

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

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

6. Availability of formalin-fixed paraffin-embedded (FFPE) tumour block (preferred) or at least 17 unstained slides, collected ≤ 3 months prior to randomisation, with an associated pathology report, if available. If a tumour sample taken within 3 months before randomisation is not available, and a tumour biopsy is not clinically feasible, the primary surgical resection sample or the most recent FFPE tumour biopsy sample may be used. Of these additional options, the most recent sample should be used.
 - a. The tumour tissue should be of good quality based on total and viable tumour content and must be evaluated centrally for PD-L1 expression prior to enrolment. Patients whose tumour tissue is not evaluable for prospective central testing are not eligible.
 - b. If multiple tumour specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1 testing, and the score measured in the most recent sample prior to enrolment will be used as the PD-L1 score for patient stratification.
 - i. Acceptable samples include core needle biopsies for deep tumour tissue (more than one core if clinically feasible) or excisional, incisional, punch, or

forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

- ii. Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.
 - iii. Tumour tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
 8. Life expectancy ≥ 12 weeks
 9. Measurable disease, as defined by RECIST v1.1. (Note: Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.)
 10. Adequate haematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment (Cycle 1, Day 1):
 - a. Absolute neutrophil count (ANC) ≥ 1500 cells/ μL (without granulocyte colony stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1)
 - b. Lymphocyte count $\geq 500/\mu\text{L}$
 - c. Platelet count $\geq 100,000/\mu\text{L}$ (without transfusion within 2 weeks prior to Cycle 1, Day 1)
 - d. Haemoglobin ≥ 9.0 g/dL
Patients may be transfused or receive erythropoietic treatment to meet this criterion.
 - e. Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase $\leq 2.5\times$ the upper limit of normal (ULN), with the following exceptions:
 - i. Patients with documented liver metastases: AST and ALT $\leq 5\times$ ULN
 - ii. Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5\times$ ULN
 - f. Serum bilirubin $\leq 1.25\times$ ULN
Patients with known Gilbert's disease who have serum bilirubin level $\leq 3\times$ ULN may be enrolled.
 - g. International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) $\leq 1.5\times$ ULN
This applies only to patients who are not receiving an anticoagulant medicinal product; patients receiving an anticoagulant medicinal product should be on a stable dose and have an INR which is not above the target therapeutic range.
 - h. Calculated creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault).
 11. Negative human immunodeficiency virus (HIV) test at screening.
 12. Negative hepatitis B surface antigen (HBsAg) test at screening.
 13. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive HBcAb

test followed by a negative hepatitis B virus (HBV) DNA test at screening.

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

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

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

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

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

Examples of contraceptive methods with a failure rate of $\leq 1\%$ per year include bilateral tubal ligation, male sterilisation, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

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

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

- a. With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of paclitaxel. Men must refrain from donating sperm during this same period.
- b. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

Cancer-Specific Exclusion Criteria

1. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for at least 2 weeks prior to randomisation
2. Known central nervous system (CNS) disease, except for treated asymptomatic CNS

metastases, provided all of the following criteria are met:

- a. Measurable disease outside the CNS
- b. Metastases are limited solely to cerebellar and supratentorial lesions (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
- c. No ongoing requirement for corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed)
- d. No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomisation
- e. No evidence of progression or haemorrhage after completion of CNS directed therapy

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

3. Leptomeningeal disease
4. Uncontrolled pleural effusion, pericardial effusion, or ascites (Note: patients with indwelling catheters, such as PleurX[®] are allowed)
5. Uncontrolled tumour-related pain
 - a. Patients requiring narcotic pain medication must be on a stable regimen at study entry.
 - b. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomisation. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
 - c. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomisation.
6. Uncontrolled hypercalcemia (>1.5 mmol/L [>6 mg/dL] ionized calcium or serum calcium [uncorrected for albumin] >3 mmol/L [>12 mg/dL] or corrected serum calcium > ULN) or clinically significant (symptomatic) hypercalcemia.

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

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

General Medical Exclusion Criteria

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

syndrome).

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

- a. Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded.
- b. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimised in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

11. Presence of an abnormal electrocardiogram (ECG) that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, evidence of prior myocardial infarction, or QT interval corrected using Fridericia's formula (QTcF) > 470 ms demonstrated by at least two consecutive ECGs.

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

13. Major surgical procedure within 4 weeks prior to randomisation or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis. Note: Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

14. Treatment with investigational therapy within 30 days prior to initiation of study treatment.

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

Exclusion Criteria Related to Atezolizumab

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

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

18. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis (MS), vasculitis, or glomerulonephritis. (Note: Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.)

19. Prior allogeneic stem cell or solid organ transplantation

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

History of radiation pneumonitis in the radiation field [fibrosis] is permitted.)

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

22. Active tuberculosis.

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

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

24. Prior treatment with CD137 agonists, anti-PD-1, or anti-PD-L1 therapeutic antibody or immune checkpoint targeting agents.

25. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]-2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to randomisation.

26. Treatment with systemic immunosuppressive medications (including but not limited to corticosteroids, cyclophosphamide, azathioprine, cyclosporine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to randomisation, or anticipated requirement for systemic immunosuppressive medications during the trial.

- a. Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study.
- b. Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumour assessments performed using MRI.
- c. The use of corticosteroids (≤ 10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
- d. Systemic corticosteroids are allowed as paclitaxel premedication during the trial at a dose ≤ 10 mg dexamethasone or equivalent in order to avoid severe hypersensitivity reactions.

27. Poor peripheral venous access

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

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

Exclusion Criteria Related to Paclitaxel

30. History of hypersensitivity reactions to paclitaxel or other drugs formulated in the

same solvent as paclitaxel (polyoxyethylated castor oil).

End of Study

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

Global Study

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

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

China Population

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

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

Length of Study

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

Investigational Medicinal Products

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

Atezolizumab (Investigational Drug)

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

Placebo (Comparator)

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

Patients will receive atezolizumab 840 mg (corresponding to 14 mL from drug product, in 250 mL 0.9% sodium chloride [NaCl]) or matching placebo by IV infusion administered on Day 1 and Day 15 (\pm 3 days) of every 28-day cycle. The first dose (Cycle 1, Day 1) will be administered over 60 (\pm 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (\pm 10) minutes.

For the first infusion of atezolizumab/placebo, no premedication will be administered. Should the patient experience infusion-related reaction(s) during any infusion, premedication with antihistamines may be administered for subsequent infusions at the discretion of the treating physician.

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

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

Paclitaxel (Background Chemotherapy)

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

Paclitaxel will be administered at the 90 mg/m² dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. In the absence of unacceptable toxicity, paclitaxel will be administered until PD or until the end of the study, whichever occurs earlier.

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

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

Patients may be treated with dexamethasone ≤10 mg IV within 1 hour prior to the paclitaxel infusion if the patient did not take the oral dexamethasone.

- Diphenhydramine 50 mg IV (or equivalent) 30-60 minutes prior to the paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30-60 minutes prior to paclitaxel infusion.

Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumour immune activity, it is recommended that the dose of dexamethasone (or equivalent) is minimised to the extent that is clinically feasible. For example, if paclitaxel is well tolerated during the first two weekly infusions without apparent hypersensitivity reaction, a reduction in the dose of dexamethasone premedication (or equivalent) should be considered for subsequent cycles if permitted by institutional standard of care. This approach has been reported to be successful in the literature ([Berger et al. 2012](#)).

Details on paclitaxel dose modifications due to toxicity are provided in Section [5.1.5.3.2](#).

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

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

Non-Investigational Medicinal Products

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

Statistical Methods

Primary Analysis

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

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

PFS will be tested hierarchically in the following fixed order:

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

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

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

The final analysis of the primary endpoint (PFS) in the China population will be conducted after approximately 36 PFS events have been documented in the China population with PD-L1-positive tumour status. Methods for analysing data from the China population will be provided in the Statistical Analysis Plan (SAP). Results from these analyses will be summarised in a separate report from the clinical study report (CSR) for the Global study.

Further details will be provided in the SAP.

Determination of Sample Size

Global Study

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

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

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

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

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

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

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

Further details will be included in the SAP.

China Population

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

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

Further details will be included in the SAP.

Interim Analyses

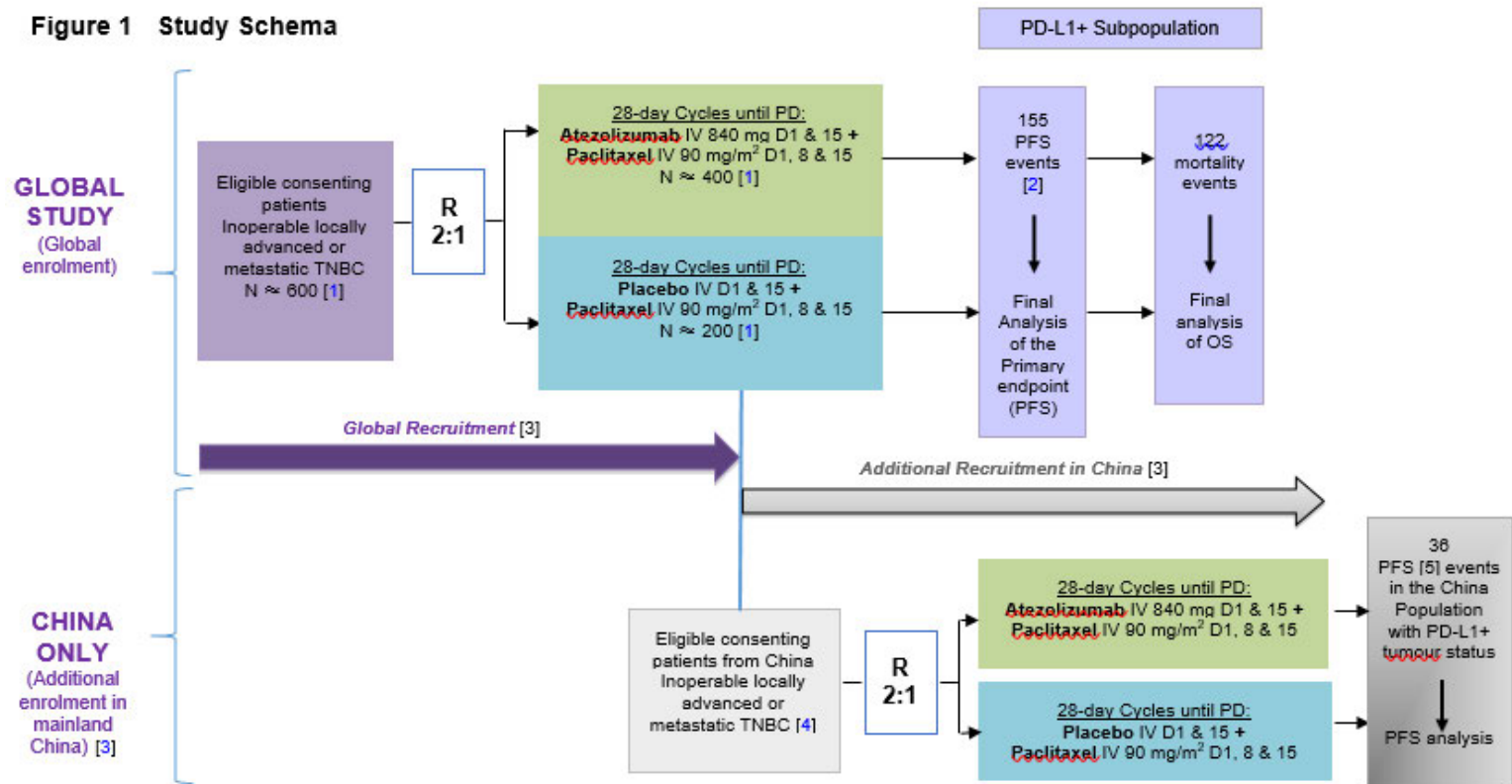
No interim analysis of PFS is planned.

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

The iDMC will complete periodic reviews of safety data.

Appendix 2 Study Schema

Figure 1 Study Schema



D=day; IV= intravenous; PD= disease progression; R = randomisation; RECIST=Response Evaluation Criteria in Solid Tumors; TNBC=triple-negative breast cancer

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

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

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

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

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

Appendix 3 Schedule of Assessments

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

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

Appendix 3 Schedule of Assessments (cont.)

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

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

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

[a3] Paclitaxel will be administered at the 90 mg/m² dose via 1-hour IV infusion on Days 1, 8, and 15 of every 28-day cycle. Paclitaxel should not be administered more frequently than every 7 days. The Day 8 visits are not required for patients who have discontinued paclitaxel and are continuing treatment with atezolizumab/placebo only.

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

[c] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomisation. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomisation (except where otherwise specified) may be used for screening assessments rather than repeating such tests. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

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

[g] Tumour assessments will be performed every 8 weeks for the first 12 months following randomisation, and every 12 weeks thereafter, until PD, death, withdrawal of consent, or study termination by the Sponsor (whichever occurs first). All measurable and evaluable lesions should be assessed and documented at screening/baseline. Radiologic imaging performed during the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan, 3) CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis, and 4) any other imaging studies (CT neck, plain films, etc.) as clinically indicated/determined by the treating physician. An MRI scan of the brain is required to confirm or refute a diagnosis of CNS metastasis at screening in the event of an equivocal scan. For each patient, the same radiographic procedures and technique must be used throughout the study, and results must be reviewed by the investigator before dosing at the next cycle. Tumour response will be

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

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

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

[i] Complete physical examination at Screening, and EOT, and symptom-driven physical examinations within 96 hours before Day 1 of each cycle, and as clinically indicated. Physical examinations will include a review of the main body organs and systems, with special attention to cardiovascular (e.g. abnormally low or irregular pulse, chest pain, tachycardia, swollen legs), respiratory (e.g. shortness of breath, crackling), gastrointestinal (e.g. abdominal pain, digestive disorders) systems, and a neurological exam focusing on signs and symptoms potentially indicative of disorders such as myasthenia gravis, motor and sensory neuropathy, meningitis, and encephalitis.

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

[k] Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. At all clinic visits where study treatment is administered, vital signs should be determined within 60 minutes before the first infusion. Vital signs will also be determined during and after the infusions if clinically indicated.

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

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

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

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

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

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

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

[s] See [Appendix 2](#) for a detailed schedule.

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

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

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

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

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

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

[z] All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information until death, withdrawal of consent, loss to follow-up, or until study termination by the Sponsor. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months ± 21 days. Public information sources (e.g., county records) may also be used to obtain information about survival status only in case the patient withdrew from the study. Information regarding PFS2 and PROs will also be collected during the survival follow-up period.

Appendix 4 Anti-Drug Antibody, Pharmacokinetic, Pharmacodynamic, and Exploratory Biomarker Sampling Schedule

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

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

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

- [a] Samples for atezolizumab PK and ADA will be collected from patients enrolled in the Global Study during the first four cycles of atezolizumab/placebo and at the Treatment discontinuation visit. For patients who discontinue atezolizumab/placebo and continue on paclitaxel alone, the scheduled collection for atezolizumab PK at the treatment discontinuation visit is still required. Patients enrolled in mainland China will not undergo atezolizumab PK and ADA assessments.
- [b] Samples for paclitaxel PK were collected from the first approximately 60 patients randomised in the Global Study (Arm A and Arm B). No further sampling for paclitaxel PK will occur in the study. Patients enrolled in mainland China will not undergo paclitaxel PK assessments.
- [c] Results of PD-L1 testing of this mandatory baseline tumour sample must be obtained from the designated central laboratory prior to enrolment. The screening sample must have been collected \leq 3 months from randomisation. If a tumour sample taken within 3 months before randomisation is not available and a tumour biopsy is not clinically feasible, the primary surgical resection sample or the most recent FFPE tumour biopsy sample may be used. Of these additional options, the most recent sample should be used.
- [d] Mandatory whole blood for germline DNA isolation will be collected during the Baseline visit. If this sample has not been collected during the Baseline visit, it can be collected at any of the following cycles.
- [e] On-treatment tumour samples for biomarker analyses are optional. They must be collected within 14 days prior to treatment on Day 1 of Cycle 2 and at disease progression (\pm 7 days) only if deemed clinically feasible by the Investigator.
- [f] Whole blood samples collected at Day 1 of Cycle 1, Day 1 of Cycle 2 and at disease progression are to assess peripheral blood mononuclear cells (PBMCs). Whole blood samples for PBMC analysis have been collected from over 300 patients at baseline; for these patients, sample collection will continue as described in the above table (on C2D1 and at PD). However, for newly enrolled patients, there will be no whole blood sampling for PBMC analysis at any time-point. Patients enrolled in China will not undergo this biomarker assessment.