Official Title: A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer

NCT Number: NCT02425891

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH NAB-PACLITAXEL COMPARED WITH PLACEBO WITH NAB-PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
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VERSION NUMBER:	1
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STATISTICAL ANALYSIS PLAN APPROVAL

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1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the analyses that are planned to be performed for the Clinical Study Report of Study WO29522 (IMpassion130).

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

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

2.2 OUTCOME MEASURES

See the protocol synopsis in Appendix 1 for a description of the outcome measures.

2.3 DETERMINATION OF SAMPLE SIZE

Up to 900 patients in total will be randomized into the study.

2.3.1 Type I Error Control

The type I error (α) for this study is 0.05 (two-sided). Type I error will be controlled for the following efficacy endpoints:

- Co-primary efficacy endpoint of investigator-assessed progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (intent to treat [ITT] and programmed death-ligand 1 [PD-L1]–selected subgroups).
- Co-primary efficacy endpoint of overall survival (OS) (ITT and PD-L1–selected subgroups).
- Secondary efficacy endpoint: Investigator-assessed objective response rate (ORR) by RECIST v1.1 (measurable disease population).

Type I error will be controlled by comparing these endpoints between treatment arms according to the following testing procedure (Figure 1).

At the time of the analysis of PFS, the co-primary endpoints of PFS and OS and the secondary endpoint of ORR are tested in the ITT population and in the PD-L1–selected subpopulation, as follows:

1. α (0.05) will be allocated between PFS (0.01) and OS (0.04) . The allocated type I error for PFS is further allocated to PFS in the ITT (0.005) and PFS in the PD-L1–selected subgroup (0.005).

Testing of PFS and ORR

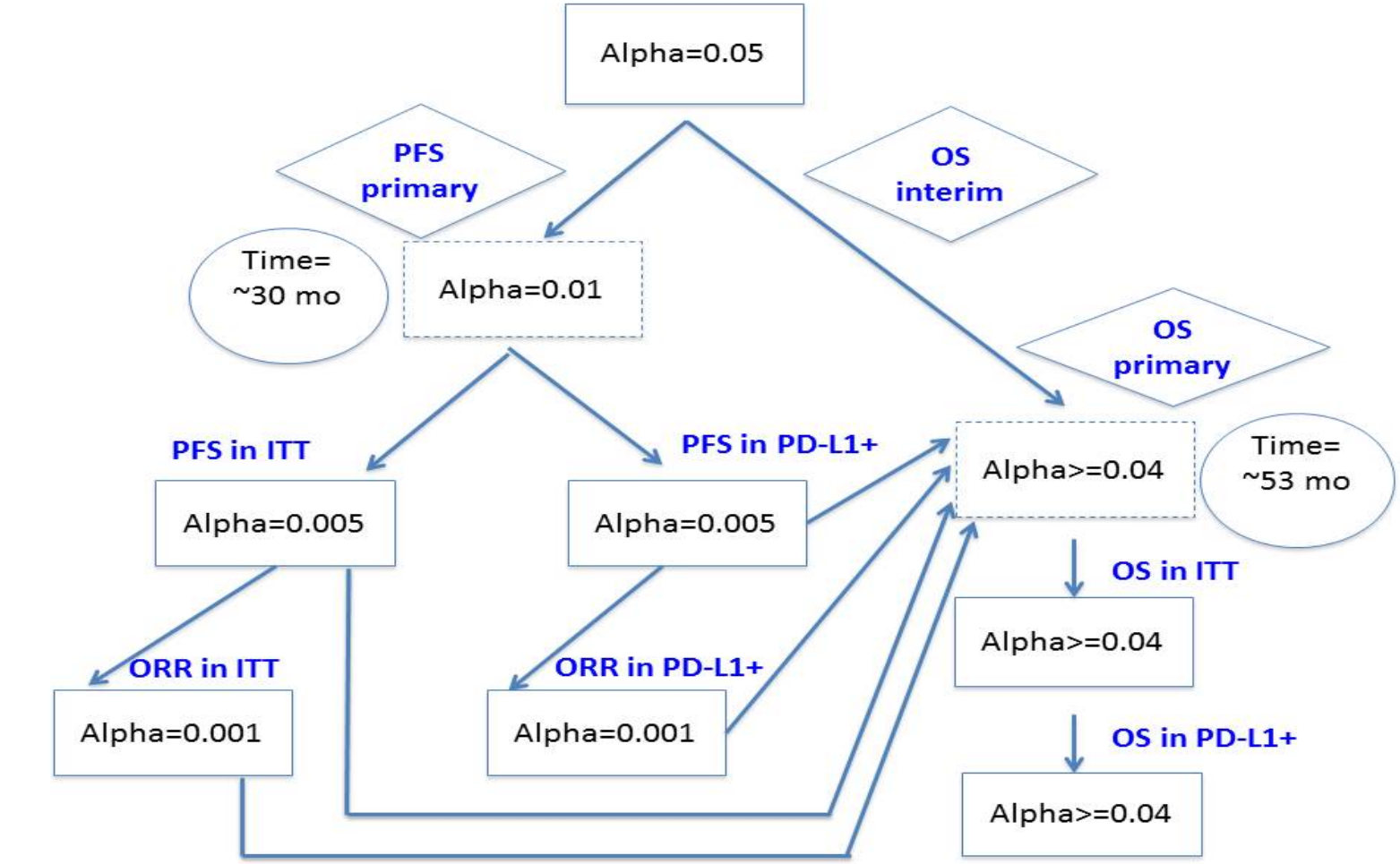
2. Test the null hypothesis of no difference in PFS between the two arms using the stratified log-rank test in the ITT population and the PD-L1–selected subgroup with the allocated type I error.

3. If one or both of the null hypotheses from the step above is rejected, ORR will subsequently be compared between the two arms in the corresponding populations (one or both) using the stratified Cochran-Mantel-Haenszel test using a Type I error of 0.001 for each correspondingly.

Testing of OS

4. At the time of the analysis of PFS, an interim analysis of OS in the ITT (OS [ITT]) will be performed. The interim analysis of OS (ITT) will be performed regardless of the results of the analyses of PFS and ORR. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function according to the type I error allocated to the comparison of OS (ITT). Allocation of the type I error to the comparison of OS (ITT) will depend on the outcome of the testing of PFS and ORR outlined in the Steps 1–3 above. Details for the different type I error allocations to the OS (ITT) testing are provided in Appendix 4.
5. If hypothesis of no difference in OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be compared by subsequently using the same type I error used for OS (ITT) testing.

Figure 1 Overview of the Type I Error Control



ITT = intent to treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PD-L1 = programmed death-ligand 1.

2.3.2 Co-Primary Endpoint: Progression-Free Survival

The definitive analysis of the co-primary endpoint of PFS will take place when approximately 600 PFS events (67% of 900; see Section 4.4.1.1), have occurred in the ITT population on the basis of the following assumptions:

- Two-sided, stratified log-rank test at the 0.005 significance level (two-sided) in the ITT population.
- Approximately 95% power for PFS in ITT population.
- Median PFS of 6 months in the placebo + nab-paclitaxel arm and 10 months in the atezolizumab + nab-paclitaxel arm (corresponding to a hazard ratio [HR] of 0.6) in the ITT population.
- Two-months initial delay in the onset of the treatment effect.
- Five percent annual loss to follow-up for PFS.
- No interim analysis for PFS in the ITT population.

Accrual is projected to occur over 26 months. On the basis of these assumptions, the required number of PFS events in the ITT population is projected to occur at Month 30. Also on the basis of these assumptions, it is projected that an observed HR of 0.72 or better will result in a statistically significant difference between the treatment arms (i.e., HR = 0.72 will be the minimally detectable difference for the analysis; this corresponds to an improvement of 2.3 months in median PFS from 6 months in the placebo + nab-paclitaxel arm to 8.3 months in the atezolizumab + nab-paclitaxel arm).

At this time point, a definitive analysis of PFS and an interim analysis on OS are additionally conducted in the PD-L1–selected subgroup. Assuming a PD-L1–selected rate of 40% in the enrolled population and assuming a median PFS of 6 months in the placebo + nab-paclitaxel arm and 12 months in the atezolizumab + nab-paclitaxel arm (corresponding to a HR of 0.5) in the PD-L1–selected subgroup, it is predicted that there will be about 215 PFS events (59.8% of 360). This corresponds to a power of about 75% and a minimally detectable difference of HR = 0.57 (corresponding to an increase of about 4.5 months from 6 months to 10.5 months).

2.3.3 Co-Primary Endpoint: Overall Survival

The timing and the two interim analyses and the final analysis for OS depends on the results of the definitive analysis of the co-primary endpoint PFS as well as the secondary endpoint ORR as described in Appendix 4, where the pre-specified boundaries for the different scenarios are also presented.

The final analysis will take place around 56 months after first patient in (FPI), when approximately the pre-planned number of deaths will have been observed based on the following assumptions:

- Two-sided, stratified log-rank test at the 0.05 significance level (two-sided) in the ITT population.
- Approximately 88% power for OS in ITT population.
- Median OS of 16 months in the placebo + nab-paclitaxel arm and 20.5 months in the atezolizumab + nab-paclitaxel arm (corresponding to an HR of 0.78) in the ITT population.
- Assumption of proportionality.
- 5% annual loss to follow-up for OS.
- Two interim analyses, at approximately 50% and 80% of the information fraction (see Appendix 4 for details).

Accrual is projected to occur over 26 months. On the basis of these assumptions, the required number of OS events in the ITT population is projected to occur in Month 56 ($\alpha = 0.05$; Month 62 if $\alpha = 0.04$).

If the null hypothesis of no difference of OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be tested with the same α as OS in the ITT population. Again assuming a PD-L1–selected rate of 40% and assuming a median OS of 16 months in the placebo + nab-paclitaxel arm and 22.5 months in the atezolizumab + nab-paclitaxel arm (corresponding to a HR of 0.71) in the PD-L1–selected subgroup, it is predicted that there will be about 251 ($\alpha = 0.05$; 268 if $\alpha = 0.04$) OS events in this subgroup. This corresponds to a power of about 76%.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization occurs in a 1:1 ratio using a permuted-block randomization method. Patients are randomized to one of two treatment arms: Atezolizumab + nab-paclitaxel or placebo + nab-paclitaxel. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the baseline characteristics of the following stratification factors:

- Presence of liver metastases (yes vs. no).
- Prior taxane treatment (yes vs. no).
- Tumor PD-L1 status (tumor-infiltrating immune cell score [IC] 0 vs. IC 1/2/3).

3.2 INDEPENDENT REVIEW COMMITTEE

The 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 (IRC). An independent imaging group will be used to evaluate tumor assessments for determination of progression and response rate according to RECIST v1.1 for the primary analysis. Imaging studies (computed tomography [CT]/magnetic resonance imaging [MRI]/bone scans) will be acquired according to a standard protocol and will be forwarded to the independent reviewers. In addition, relevant clinical data (randomization and treatment start date, radiological treatment information) will be forwarded, if available, to the independent reviewers to aid with assessment of progressive disease and response. Investigator tumor assessments will not be reconciled with the IRC tumor assessments. Further details will be included in the IRC Charter. Details of imaging handling procedures are also described in a separate laboratory manual.

3.3 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on a periodic basis. Members of the iDMC will be external to 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 to review unblinded safety and study conduct data prepared by an independent Data Coordinating Center (iDCC). The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Following each data review, the iDMC will provide recommendations to the Sponsor as to whether the study should continue or be amended, or whether the study should be stopped on the basis of safety (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 on the basis of the iDMC's recommendations. The final decision will rest with the Sponsor.

Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

There are two interim analyses planned for the co-primary endpoint OS. No interim efficacy analysis is planned for the co-primary endpoint of PFS. The final analysis of PFS will occur at the time of the first OS interim analysis. The first interim analysis of OS together with the final analysis of PFS, and if necessary, the second interim analysis, will be carried out by the iDCC in a blinded fashion and provided to the iDMC. The iDMC will review these data and will recommend or not recommend to release the trial results and to unblind the study to the sponsor. The DRB of the sponsor will either accept or reject this recommendation. 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 are defined as follows:

- The ITT population is defined as all randomized patients, whether or not the assigned study treatment was received.
- The PD-L1–selected subpopulation is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.
- The ORR-evaluable population is defined as patients in the ITT population with measurable disease at baseline.
- The PD-L1–ORR-evaluable population is defined as patients in the PD-L1–selected subpopulation with measurable disease at baseline.
- The duration of response (DOR)-evaluable population is defined as patients with an objective response.
- The patient-reported outcome (PRO)-evaluable population is defined as patients in the ITT population with a baseline and ≥1 post-baseline PRO assessment.
- The safety-evaluable population is defined as patients who received any amount of any study drug.
- The pharmacokinetic (PK)-evaluable population is defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

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

For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including cases in which atezolizumab was received in error.

4.2 ANALYSIS OF STUDY CONDUCT

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

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

Demographics, baseline disease characteristics and breast cancer history will be compared between both treatment arms for the ITT population. Descriptive baseline

summaries of continuous data will present the group mean, standard deviation, median, ranges and inter-quartile ranges. Descriptive baseline summaries of discrete data will present the category counts as frequencies and percentages.

The baseline value of any efficacy variable will be defined as the last available value recorded prior to randomization.

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

Previous and concomitant cancer therapy will also be summarized, including radiotherapy and surgery, as well as subsequent anti-cancer therapy. Previous and concurrent diseases and medications will also be summarized.

4.4 EFFICACY ANALYSIS

4.4.1 Co-Primary Efficacy Endpoints

4.4.1.1 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments, per RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization.

For U.S. registrational purposes, PFS will be defined as described above with an additional censoring rule for missed visits. 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.

Progression-free survival will be analyzed simultaneously in the ITT and PD-L1–selected subgroup (see Section 2.3.1). The following analyses will be performed for both PFS endpoints described above:

- Treatment comparisons will be based on the stratified log-rank test. The stratification factors will be those used for randomization (see Section 3.1) and will be obtained from the interactive Web/phone response system IxRS. Results from an un-stratified analysis and a stratified analysis with stratification factors based on the eCRF will also be provided.
- The HRwill 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 un-stratified 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).

4.4.1.2 Overall Survival (OS)

Overall survival is defined as the time from the date of randomization to the date of 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. Testing of OS is outlined in Section 2.3.1 and analysis of OS is performed analogously to PFS. OS is hierarchically tested in the ITT and PD-L1–selected subgroup (see Section 2.3.1).

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Objective Response Rate

An objective response is defined for patients with measurable disease at baseline who achieved a documented unconfirmed response [i.e., either a partial response (PR) or a complete response (CR)] on the basis of investigator assessment using RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumor assessment, will be considered as non-responders. Objective response rate is defined as the proportion of patients with measurable disease at baseline who have an objective response.

Objective response rate 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. ORR is simultaneously assessed in the ITT and PD-L1–selected subgroup with measurable disease at baseline (see Section 2.3.1).

The remaining secondary endpoints (duration of objective response and time to deterioration (TTD) in Global Heath Status [GHS]/Health-Related Quality of Life [HRQoL]) will not be adjusted for multiple testing and are based on a non-randomized subset of patients.

4.4.2.2 Duration of Objective Response

Duration of response is defined for patients who had an objective response as the time from the first occurrence of a documented unconfirmed response (CR or PR) to the date of disease progression on the basis of investigator assessment using RECIST v1.1 or death from any cause, whichever occurs first. 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 the objective response (CR or PR), patient will be censored at the date of the first occurrence of the objective response.

The analysis of DOR based on a non-randomized subset of patients (those who achieved an unconfirmed response); therefore, no formal hypothesis testing will be performed. 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.

4.4.2.3 Time to Deterioration in Global Heath Status/Health-Related Quality of Life

The primary patient-reported endpoint is the TTD in GHS/ HRQoL. 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.

Only patients with baseline and ≥ 1 post-baseline GHS/HRQoL scores will be included in the analysis. Patient-reported outcome (PRO) completion rates will be summarized at each timepoint by treatment arm. Time to deterioration 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 this time-point.

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

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 EORTC Data

Summary statistics (mean, standard deviation, median, and range) and mean change from baseline of linearly transformed absolute scores will be calculated for all items and scales of the EORTC QLQ-C30 and QLQ-BR23 at each assessment timepoint for each arm. The mean change from baseline (and 95% CI) will be assessed on patients with at least one post-baseline measurement to further inform TTD in HRQoL and of patients' treatment experience. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and disease/treatment-related symptoms scales (Osoba et al. 1998; Cocks et al. 2011).

A 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. Deterioration in function will be assessed using the published corresponding MIDs by Cocks et al. (2011). Patients who do not achieve an MID on the basis of published thresholds will be censored at the last time PRO data are available and only patients with baseline scores will be included. Patients without at least one post-baseline assessment will be censored at the date of randomization. A stratified log-rank test will be used to test the differences between treatment arms.

A longitudinal analysis will be conducted to estimate the effect difference on PRO repeated responses over a selected period of time and between the treatment arms, and mixed models on a set of covariates (baseline domain score, patient demographic, and clinical variables) will be conducted. Change from baseline at subsequent cycles will be presented by treatment arm and will include least squares mean (LS Mean), difference in LS Mean between two treatment arms, and 95% confidence intervals for the differences. The standard error (SE) will also be calculated for each LS Mean.

The EORTC QLQ-C30 and QLQ-BR23 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). Missing data will be assessed and reported by cycle. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

4.4.3.2 Health Economic Data

Health economic data, as assessed by the EQ-5D-5L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-5L assessment. The results from the health economic data analysis will be reported separately from the clinical study report.

4.4.3.3 Biomarker Analysis

Exploratory biomarker analyses (in tumor tissues and plasma, whole blood, or serum) will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. Results will be presented in a separate report.

4.4.4 Sensitivity Analyses

4.4.4.1 Sensitivity Analyses of Progression-Free Survival

Censoring for non-protocol therapy

Non-protocol therapy is defined as any anti-cancer therapy other than study treatment that typically is the subsequent line of therapy. The impact of NPT on the co-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 before the patient received NPT.

PFS by IRC

An analysis of PFS on the basis of the IRC assessments will be performed using the same methodology as specified for PFS on the basis of investigator assessment.

Additional sensitivity analyses may be considered if appropriate.

4.4.4.2 Sensitivity Analyses of Overall Survival

Accounting for second-line immunotherapy use

Quickly evolving development of checkpoint inhibitors may lead to increased PD-1/PD-L1 treatment options for patients in the second-line triple-negative breast cancer, 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 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 subsequent line of therapy. Censoring for treatment switching will be applied to OS, analogue to censoring for NPT for PFS, see above.

Rank-preserving structural failure time (RPSFT) method

The rank-preserving structural failure time (RPSFT) method was introduced by Robins and Tsiatis (1991). It provides an estimate of the overall survival time for the placebo arm had treatment switching not occurred. It estimates overall survival 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.

Inverse Probability of Censoring Weighting method

The inverse probability of censoring weighting (IPCW) method is discussed by Robins and Finkelstein (2000). Inverse probability of censoring weighting (IPCW), like the censoring at treatment switch method, does not use any data collected after treatment switching. Assuming only control patients switch treatment, the method censors patients at switch and uses the control arm patients to create weights that represent how similar a patient who didn't switch is to a patient who did switch. This weighted data then creates a pseudo population that would have been observed if censoring at treatment switching had not occurred (also known as a counterfactual population) by giving increased weight to non-censored patients with similar characteristics to censored patients. These time varying weights are then included into the analysis (e.g., in a Cox model or log-rank test) so that the final analysis is corrected for the effect of treatment switching.

This approach includes a time-dependent indicator of treatment switching, with time-dependent propensity-score weighting based on modeling the time-to- treatment-switching via Cox models utilizing baseline and time-dependent covariates.

The following baseline and time-dependent covariates will be included in the time-to-treatment-switching Cox model. Baseline covariates include age and the stratification factors presence of liver metastases (yes vs. no), and prior taxane treatment (yes vs. no). Time-dependent covariates include treatment discontinuation ($=1$ after treatment discontinuation and 0 otherwise) and tumor PD-L1 status (tumor-infiltrating immune cell score [IC] 0 vs. IC 1/2/3) (measured at baseline and progression). If less than 15% of patients in the atezolizumab + nab-paclitaxel arm receive a second line of another immunotherapy, the stabilized weights are set to one for all atezolizumab + nab-paclitaxel patients for stabilization of the analysis.

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 using the same methodology as specified for ORR on the basis of investigator assessment. Measurable disease at baseline is according to 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 using the same methodology as specified for DOR on the basis of investigator assessment. Objective response is according to the assessment by the IRC.

4.4.5 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, PFS, ORR, and OS in these subgroups will be examined. 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. Objective response rate will be summarized for each level of the categorical variables.

4.5 PHARMACOKINETIC ANALYSIS

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

Plasma concentrations of nab-paclitaxel (reported as total paclitaxel) will be measured where applicable (see Appendix 3). The concentration data will be summarized with use of descriptive statistics as stated above.

Additional PK analyses may be conducted if deemed appropriate.

4.6 SAFETY ANALYSES

All safety analyses will be performed on the Safety Population, i.e. all patients who receive any dose of study medication (see Section 4.1). Non-overlapping visit windows will be assigned to post-baseline assessments, e.g., assessments falling between Days 22 and 32 will be reported under Week 4.

4.6.1 Exposure of Study Medication

Study treatment (atezolizumab, placebo and nab-paclitaxel) exposure, including treatment duration, dose intensity, number of cycles and total cumulative dose will be summarized with descriptive statistics. The number of missed doses will also be displayed. Reasons for discontinuation from study treatment will be summarized.

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 mapped term, appropriate thesaurus level and NCI CTCAE grade.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported, e.g. serious adverse events related to invasive procedures such as biopsies.

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until the initiation of non-protocol anti-cancer therapy after the last administration of study drug, whichever occurs first. After this period, investigators should report any serious adverse events (SAEs) and adverse events of special interest (AESI) that are believed to be related to prior treatment with study drug.

Summary tables of the following will be provided:

- SAEs
- AEs leading to study treatment discontinuation
- AEs leading to dose reduction or interruption
- Treatment-related AEs
- Severe adverse events (Grade 3 or higher)
- AEs leading to death
- AEs by highest NCI CTCAE Grade
- Sponsor-defined AESI

A summary table of common AEs, i.e., those occurring in at least 10% of patients, will be provided.

Adverse events of special interest for this study, as defined in the study protocol, include the following conditions which may be suggestive of an autoimmune disorder:

- Pneumonitis
- Grade ≥ 3 hypoxia or dyspnea
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency
- Vasculitis
- Hepatitis
- Grade ≥ 2 transaminitis (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN or AST/ALT $> 10 \times$ ULN)
- Systemic lupus erythematosus
- Guillain-Barre Syndrome
- Skin reactions: vitiligo, pemphigoid

Other AESI for this study, as defined in the study protocol, include:

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome (SIRS), or infusion-reaction syndromes.
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6, Abnormal Liver Function Tests).
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Multiple occurrences of the same event will be counted once at the maximum severity. All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the data cutoff date.

All deaths and causes of death will be summarized.

4.6.3 Laboratory Data

Laboratory data will be classified according to NCI CTCAE 4.0 and will be summarized descriptively over time including change from baseline. Highest NCI CTCAE grade post-baseline will also be reported and shift tables from baseline to worst value during the study post-baseline will be presented.

A Hy's law analysis will be provided. The potential Hy's law quadrant is defined as ALT or AST increases above 3-fold the upper limit of normal (ULN) with concomitant total bilirubin increases above 2-fold the ULN.

4.6.4 Anti-Therapeutic Antibody

Incidence of anti-therapeutic antibodies (ATAs) against atezolizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ATA status may be conducted to explore the potential impact of immunogenicity.

4.6.5 Vital Signs and ECOG Performance Status

Vital signs will be summarized descriptively over time including change from baseline. ECOG performance status will also be summarized over time.

4.6.6 Electrocardiograms

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

4.7 INTERIM ANALYSES

4.7.1 Progression-Free Survival

There are no planned interim analyses of the co-primary endpoint of PFS.

4.7.2 Overall Survival

A total of three analyses of OS will be performed (two interim analyses and one final analysis). The timing of the two interim analyses and the final analysis for OS depends on the results of the definitive analysis of the co-primary endpoint PFS as well as the secondary endpoint ORR as described in Appendix 4, where the pre-specified boundaries for OS of all different scenarios are also presented (see Section 2.3.1).

The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function (DeMets and Lan 1994).

4.7.3 Safety Monitoring

The iDMC will convene to review interim safety analysis results. See Section 3.3 for additional details regarding the iDMC.

4.7.4 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one additional interim efficacy analysis for OS. The specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed are outlined below.

The Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

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, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained.

5. REFERENCES

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Appendix 1
Protocol Synopsis

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH NAB-PACLITAXEL COMPARED WITH PLACEBO WITH NAB-PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	WO29522
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-005490-37
IND NUMBER:	123,277
TEST PRODUCT:	Atezolizumab
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 of atezolizumab with nab-paclitaxel compared with placebo with nab-paclitaxel in patients with metastatic or locally advanced triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (mBC). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

The following efficacy objectives will be evaluated in both the intent-to-treat (ITT) population (i.e., all randomized patients) and the subpopulation with programmed death–ligand 1 (PD-L1)–selected tumor status.

The co-primary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel as measured by PFS
- To evaluate the efficacy of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel as measured by overall survival (OS)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel as measured by objective response rate (ORR; per investigator assessment using RECIST v1.1)
- To evaluate the efficacy of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel as measured by duration of objective response (DOR; per investigator using RECIST v1.1) among patients with an objective response

Appendix 1
Protocol Synopsis (cont.)

- To evaluate patient-reported outcomes (PROs) of health status/health-related quality of life (HRQoL) associated with atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel, as measured by the time to deterioration (TTD) in Items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, pharmacodynamics, safety, and efficacy

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the pharmacokinetics of atezolizumab when administered with nab-paclitaxel
- To characterize the pharmacokinetics of nab-paclitaxel when administered with atezolizumab

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23)
- To evaluate health utility as measured by the EuroQoL 5 Dimension (EQ-5D-5L) questionnaire for health economic modeling of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel
- To assess predictive, prognostic, and pharmacodynamic (PD) exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment

Study Design

Description of Study

This is a Phase III, global, multicenter, double-blind, two-arm, randomized, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab administered with nab-paclitaxel compared with placebo in combination with nab-paclitaxel in patients with locally advanced or metastatic TNBC who have not received prior systemic therapy for mBC.

Eligible patients will be randomized in a 1:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Randomization will be stratified by the following three factors: presence of liver metastases (yes vs. no); prior taxane treatment (yes vs. no); and tumor PD-L1 status (IC0 vs. IC1/2/3).

In the absence of disease progression or unacceptable toxicity, nab-paclitaxel will be administered for a target of at least 6 cycles, with no maximum. nab-Paclitaxel and atezolizumab or placebo may be discontinued for toxicity independently of each other in the absence of disease progression. The Sponsor, patients, and investigators will not be aware of each patient's treatment assignment prior to unblinding.

Appendix 1
Protocol Synopsis (cont.)

In order to interrogate the mechanism of action of the drug combination in the tumor microenvironment and possible resistance mechanisms, tumor tissue may be optionally collected before dosing on Cycle 2, Day 1.

To test the mechanisms of resistance to the drug combination in the tumor microenvironment, all patients will undergo a mandatory tumor biopsy collection (if clinically feasible) at first evidence of radiographic disease progression per RECIST v1.1. DNA sequencing of cancer-related genes will be performed on these specimens by Foundation Medicine, Inc. (Cambridge, MA). The research report may be obtained by the Investigator, if desired, directly from Foundation Medicine, Inc. and will describe results from investigational tests that are not intended to be used to guide future treatment decisions.

Tumor assessments per RECIST v1.1 will be performed approximately every 8 weeks (±1 week) for the first 12 months after Cycle 1, Day 1 and every 12 weeks (± 1 week) thereafter until disease progression or treatment discontinuation, whichever is later. Tumor assessments will be performed on the specified schedule regardless of treatment delays.

Treatment will be discontinued upon radiographic disease progression 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.

For estimation of PFS, ORR, and DOR, tumor response will be based on RECIST v1.1. The 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 (IRC) in the future, if necessary.

All patients will be followed for survival approximately every 3 months *after the treatment discontinuation visit* until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. In addition, information regarding use of subsequent anti-cancer agents for metastatic TNBC during the survival follow-up period will be collected.

The pharmacokinetics of atezolizumab and nab-paclitaxel will be determined.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including tumor tissues, as well as serum and plasma and whole blood, will be collected for exploratory biomarker assessments.

Number of Patients

Up to 900 patients will be enrolled at approximately 257 sites globally.

Target Population

Patients with metastatic or locally advanced TNBC who have not received prior systemic cytotoxic therapy for mBC may be eligible for this study. Locally advanced disease must not be amenable to resection with curative intent. Patients may have received prior chemotherapy in the neoadjuvant/adjuvant setting if treatment was completed ≥12 months prior to randomization. Patients must comply with all eligibility criteria to be enrolled.

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Women or men aged ≥18 years
- Metastatic or locally advanced, histologically documented TNBC (absence of HER2, ER, and PR expression)

HER2 negativity is defined as either of the following by local laboratory assessment:

Appendix 1
Protocol Synopsis (cont.)

In situ hybridization (ISH) non-amplified (ratio of HER2 to CEP17 <2.0 or single probe average HER2 gene copy number <4 signals/cell), or

IHC 0 or IHC 1+ (if more than one test result is available and not all results meet the inclusion criterion definition, all results should be discussed with the Medical Monitor to establish eligibility of the patient)

ER and PR negativity are defined as $<1\%$ of cells expressing hormonal receptors via IHC analysis.

- No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC

  Radiation therapy for metastatic disease is permitted. There is no required minimum washout period for radiation therapy. Patients should be recovered from the effects of radiation.

  Prior chemotherapy (including taxanes) in the neoadjuvant or adjuvant setting is allowable if treatment was completed ≥ 12 months prior to randomization.

- Eligible for taxane monotherapy (i.e., absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control)
- Representative FFPE tumor specimens (either an archival specimen or fresh pre-treatment tissue from relapsed disease) in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report documenting ER, PR, and HER2 negativity

  Patients with fewer than 20 unstained slides available at baseline (but no fewer than 12) may be eligible upon discussion with the Medical Monitor.

  Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated for PD-L1 expression prior to enrollment. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible.

  If multiple tumor specimens are submitted (e.g., an archival specimen and tissue from relapsed disease), patients may be eligible if at least one specimen is evaluable for PD-L1. For the purpose of stratification, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples.

  A tumor specimen obtained from relapsed metastatic or locally advanced disease (if applicable) must also be submitted, if clinically feasible.

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

  FFPE tumor specimens in paraffin blocks are preferred

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

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

- ECOG performance status of 0 or 1
- Life expectancy ≥ 12 weeks
- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.

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

  ANC ≥ 1500 cells/μL (without granulocyte colony-stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1)

  Lymphocyte count $\geq 500/\mu$L

Platelet count $\geq$ 100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

Hemoglobin $\geq$ 9.0 g/dL

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

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ the upper limit of normal (ULN), with the following exceptions:

Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

Serum bilirubin $\leq 1.25 \times$ ULN

Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

INR and aPTT $\leq 1.5 \times$ ULN

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

Calculated creatinine clearance $\geq$ 30 mL/min

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year, during the treatment period and for at least $5\ months$ after the last dose of atezolizumab/placebo or 1 month after the last dose of nab-paclitaxel, whichever is later.

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

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  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 postovulation methods) and withdrawal are not acceptable methods of contraception.

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

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of nab-paclitaxel. Men must refrain from donating sperm during this same period.

  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 postovulation methods) and withdrawal are not acceptable methods of contraception.

- Women who are not postmenopausal ($\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug

Exclusion Criteria

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

Cancer-Specific Exclusion Criteria

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization
- Known CNS disease, except for treated asymptomatic CNS metastases, provided all of the following criteria are met:

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 7 days *or whole brain radiation within 14 days* prior to randomization

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  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 without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

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

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

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomization.
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue denosumab use and replace it with a bisphosphonate instead while on study. There is no required minimum washout period for denosumab.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than TNBC within 5 years prior to randomization, 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 or basal or squamous cell skin cancer)

General Medical Exclusion Criteria

- Pregnancy or lactation
- 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)

Appendix 1
Protocol Synopsis (cont.)

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

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

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF $<$50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible.
- Major surgical procedure within 28 days prior to randomization or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis

  Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted
- Known hypersensitivity to nab-paclitaxel or to any of the excipients.

Exclusion Criteria Related to Atezolizumab

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

  Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin *dosing* regimen *are* eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area (BSA)

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study

  Patients must agree not to receive live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment, or within *5 months* following the last dose of atezolizumab/*placebo*.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the study

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study

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

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

End of Study

The end of the study is expected to occur about 53 months after FPI when approximately the pre-planned number of deaths will have been observed.

OS events will be monitored throughout the course of the study, and study timelines might be updated as indicated.

Length of Study

The end of the study is expected to occur about 53 months after FPI.

Investigational Medicinal Products

Test Products

- Atezolizumab 840-mg flat dose or placebo administered via IV infusion on Day 1 and Day 15 of every 28-day cycle
- nab-Paclitaxel 100 mg/m^2 administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. *Doses of nab-paclitaxel should not be administered more frequently than every 7 days.*

Statistical Methods

Primary Analysis

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

Appendix 1
Protocol Synopsis (cont.)

Progression-Free Survival

PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per RECIST v1.1 or death from any cause, whichever occurs first. PFS is simultaneously assessed in the ITT and PD-L1–selected subgroup.

For United States registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. 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. Type I error control will be applied to this analysis of PFS. The following analyses will be performed for both PFS endpoints described above. PFS will be compared between treatment arms with use of the stratified log-rank test. The HR for disease progression or death will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: presence of liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3). Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm.

Overall Survival

OS is defined as the time from the date of randomization to the date of death from any cause. Testing of OS is outlined in the protocol and analysis of OS is performed analogously to PFS.

OS will be analyzed in a similar manner as PFS.

Determination of Sample Size

Up to 900 patients in total will be randomized into the study.

Type I Error Control

The type I error (α) for this study is 0.05 (two-sided). Type I error will be controlled for the following efficacy endpoints:

- Co-primary efficacy endpoint of investigator-assessed PFS by RECIST v1.1 (as defined for United States registrational purposes; ITT and PD-L1–selected subgroups)
- Co-primary efficacy endpoint of OS (ITT and PD-L1–selected subgroups)
- Secondary efficacy endpoint: Investigator-assessed ORR by RECIST v1.1 (measurable disease population)

Type I error will be controlled by comparing these endpoints between treatment arms according to the following testing procedure.

At the time of the analysis of PFS, the co-primary endpoints of PFS and OS and the secondary endpoint of ORR are tested in the ITT population and in the PD-L1–selected subpopulation, as follows:

1. α (0.05) will be allocated between PFS (0.01) and OS (0.04). The allocated type I error for PFS is further allocated to PFS in the ITT (0.005) and PFS in the PD-L1–selected subgroup (0.005).

Testing of PFS and ORR

2. Test the null hypothesis of no difference in PFS between the two arms using the stratified log-rank test in the ITT population and the PD-L1–selected subgroup with the allocated type I error.
3. If one or both of the null hypotheses from the step above is rejected, ORR will subsequently be compared between the two arms in the corresponding populations (one or both) using the stratified Cochran-Mantel-Haenszel test using a Type I error of 0.001 for each correspondingly.

Appendix 1
Protocol Synopsis (cont.)

Testing of OS

4. At the time of the analysis of PFS, an interim analysis of OS in the ITT (OS [ITT]) will be performed. The interim analysis of OS (ITT) will be performed regardless of the results of the analyses of PFS and ORR. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function according to the type I error allocated to the comparison of OS (ITT). Allocation of the type I error to the comparison of OS (ITT) will depend on the outcome of the testing of PFS and ORR outlined in the Steps 1–3 above. Details for the different type I error allocations to the OS (ITT) testing are provided in the protocol.
5. If hypothesis of no difference in OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be compared by recycling the type I error used for OS (ITT) testing.

Interim Analyses

There are no planned interim analyses of the co-primary endpoint of PFS.

Overall Survival

A total of three analyses of OS will be performed (two interim analyses and one final analysis). The timing and the two interim analyses and the final analysis for OS depends on the results of the definitive analysis of the co-primary endpoint PFS as well as the secondary endpoint ORR as described in the protocol, where the pre-specified boundaries for OS of all different scenarios are also presented.

The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function..

Appendix 2
Schedule of Assessments

Assessment Window (Days)	Screening	All Cycles		Treatment Discontinuation [d]		
	Days – 28 to -1	1 [b]	8 (+3) [b,c]	15 (+3) [b]	≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s) [a]	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information [e]	x					
HIV, HBV, HCV serology [f]	x					
Concomitant medications [g]	x	x	x	x	x	
Tumor assessment [h]	x	See footnote (h)			x	x
Head CT or MRI	x					
Patient-reported outcomes [i]		x			x	x [j]
Complete physical examination [k]	x				x	
Limited physical examination [k]		x [l]				
ECOG performance status	x	x [l]			x	
Vital signs [m]	x	x	x	x	x	
12-lead electrocardiogram [n]	x	Perform as clinically indicated				
Weight	x	x			x	

Appendix 2
Schedule of Assessments (cont.)

Assessment Window (Days)	Screening	All Cycles		Treatment Discontinuation [d]		
	Days – 28 to -1	1 [b]	8 (+3) [b,c]	15 (+3) [b]		Days – 28 to -1
Height	x					
Hematology [o]	x	x [l]	x	x	x	
Serum chemistry [p]	x	x [l]	x	x	x	
Coagulation panel (aPTT, INR)	x				x	
C-reactive protein testing	x	x [l]				
Urinalysis [q,r]	x	Perform as clinically indicated				
Pregnancy test (women of childbearing potential only)	x [s]	x [t]			x [t]	
TSH, free T3, free T4	x	C1D1 & every 2nd cycle [l]			x	
Auto-antibody testing [u]		x				
Serum sample for ATA assessment [v]		x			x	x
Serum sample for atezolizumab PK sampling [v]		x			x	x
Plasma samples for nab-paclitaxel [v]		x				
Blood samples for PD biomarkers [v]		x			x	
Optional whole blood sample for RCR DNA [w]		x				
Adverse events [x]		x	x	x	x	

Appendix 2
Schedule of Assessments (cont.)

Assessment Window (Days)	Screening	All Cycles		Treatment Discontinuation [d]		
	Days – 28 to -1	1 [b]	8(+3) [b,c]	15 (+3) [b]		Days – 28 to -1
Atezolizumab/placebo infusion [y]		x		x		
Nab-paclitaxel administration		x	x	x		
Archival/fresh screening FFPE tumor tissue block or 20 unstained slides [z]	x					
Optional fresh biopsy		Cycle 2 [aa]				
Mandatory FFPE tumor tissue specimen at disease progression [bb]					x	
Survival and anti-cancer therapy follow-up [cc]						x

anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen ATA = anti-therapeutic 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; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; q8w = every 8 weeks; QLQ-BR23 = Quality-of-life Questionnaire Breast Cancer Module; QLQ-C30 = Quality-of-life Questionnaire Core 30; RCR = Roche Clinical Repository; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone; v = version.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] 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 randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to *randomization* (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.

[b] Assessment window of ± 3 days for *Day 1 of Cycles ≥2. Doses of nab-paclitaxel should not be administered more frequently than every 7 days.* If scheduled dosing is precluded because of a holiday, then dosing may be postponed to the soonest following date, with subsequent

dosing continuing on the specified schedule. After five cycles, one of three cycles may be delayed by 1 week to allow for vacations. 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.

[c] Day 8 visits are not required for patients who have discontinued nab-paclitaxel and are continuing treatment with atezolizumab/placebo alone.

[d] Patients will be asked to return to the clinic not more than 30 days after the decision to discontinue treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease progression is determined or confirmed) may be used as the treatment discontinuation visit.

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

[f] All patients will be tested for HIV locally prior to the inclusion into the study; HIV-positive patients will be excluded from the clinical study. Hepatitis B surface antigen, anti-HBc, and anti-HBs should be collected during screening and tested locally. HBV DNA must be collected prior to randomization in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

[g] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[h] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. 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, and 3) any other imaging studies (CT neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 8 weeks ($\pm$1 week) for the first 12 months following randomization, and every 12 weeks ($\pm$1 week) thereafter, with additional scans as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan if there were osseous sites of disease identified on these studies during the screening period or if these studies are felt to be clinically indicated by the treating physician, and 3) any other imaging studies felt to be clinically indicated by the treating physician. Tumor response will be evaluated using RECIST v1.1. In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first.

[i] The EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L questionnaires will be completed in order by the patient on an ePRO tablet at the site at

baseline (Cycle 1, Day 1), and then Day 1 of each subsequent cycle thereafter, at the treatment discontinuation visit*, and during survival follow-up. All PRO questionnaires scheduled for administration during a clinic visit are required to be completed by the patient at the investigational site* at the start of the clinic visit and 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 ensure measures have been completed and saved before the patient leaves the investigational site. All patients will also complete the *three* PRO questionnaires every 28 days for 1 year after treatment discontinuation, regardless of whether the patient is receiving subsequent anti-cancer therapy. Questionnaires will be completed after treatment discontinuation by the patient at home on an ePRO handheld device provisioned to the patient *at the treatment discontinuation visit*. Male patients will not complete the QLQ-BR23, as this measure has not been validated in men.

[j] Collect every 28 days *(± 3 days)* for 1 year during survival follow-up.

[k] Complete and limited physical examinations are defined in Protocol Section 4.5.2.2.

[l] ECOG performance status, limited physical examination, local laboratory assessments, and C-reactive protein assessment may be obtained ≤96 hours before Day 1 of each cycle.

[m] Vital signs include heart rate, respiratory rate, blood pressure, and temperature. On days of study treatment administration (atezolizumab, placebo, or nab-paclitaxel), the patient's vital signs should be determined up to 60 minutes before all infusions. Vital signs will also be collected during and after every infusion of atezolizumab or placebo if clinically indicated.

[n] Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[o] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Local laboratory assessment must be reviewed prior to *every* study treatment administration. Refer to Protocol Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[p] Serum chemistry includes BUN *or urea*, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. *Magnesium and phosphorus must be tested during screening; during treatment, magnesium and phosphorus should be tested as clinically indicated.* Local laboratory assessments must be reviewed prior to *every* study treatment administration. Refer to Protocol Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[q] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[r] *As clinically indicated during treatment.*

[s] Serum pregnancy test within 14 days before Cycle 1, Day 1.

Appendix 2
Schedule of Assessments (cont.)

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

[u] 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, and all samples will be analyzed centrally. Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[v] See Appendix 3 for detailed schedule.

[w] Whole blood for DNA isolation will be collected from patients who have consented to optional RCR sampling at baseline. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[x] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

[y] Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. For atezolizumab/placebo, the initial dose will be administered over 60 (± 10) minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 (± 10) minutes. For nab-paclitaxel, study drug will be administered according to the local prescribing information.

[z] Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). An FFPE block or at least 20 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Retrieval of archival tumor sample can occur outside the 28-day screening period.

[aa] For patients who have provided consent on the Consent for Optional Biopsy; optional tumor biopsy samples may be collected by core needle or excisional/punch biopsy at Cycle 2 Day 1 per investigator discretion.

[bb] Preferably, samples collected at the time of radiographic progression should be collected from growing lesions.

[cc] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months *after the treatment discontinuation visit* (±21 days) until death, loss to follow-up, or until study termination by the Sponsor. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 3 Anti-Therapeutic Antibody, TBNK, Pharmacodynamic, and Pharmacokinetic Sampling Schedule

Study Visit	Timepoint	Sample
Cycle 1, Day 1	Predose	ATA Atezolizumab PK Nab-paclitaxel PK Pharmacodynamics [b]
	30 (±10) minutes after end of atezolizumab infusion	Atezolizumab PK
Cycle 2, Day 1	Predose	ATA Atezolizumab PK [a] Pharmacodynamics [b]
Cycle 3, Day 1	Predose	ATA Atezolizumab PK [a] Nab-paclitaxel PK [a]
	5–10 minutes before the end of nab-paclitaxel infusion	Nab-paclitaxel PK [a]
	1 hour after the end of nab-paclitaxel infusion	Nab-paclitaxel PK [a]
Cycle 4, Day 1	Predose	ATA Atezolizumab PK [a]
Cycles 8 and 16 and every eight cycles thereafter, Day 1	Predose	ATA Atezolizumab PK [a]
At time of radiographic progression		Pharmacodynamics [c]
Treatment discontinuation visit	At visit	ATA Atezolizumab PK [a]
120 (±30) days after last dose of atezolizumab/placebo [d]	At visit	ATA Atezolizumab PK [a]

ATA = Anti-therapeutic Antibody, PK = Pharmacokinetic

[a] Sample collection for both atezolizumab and nab-paclitaxel PK is required as long as patients are receiving both atezolizumab or placebo and nab-paclitaxel. For patients who discontinue atezolizumab or placebo and continue on nab-paclitaxel alone, the scheduled collection for atezolizumab PK at the treatment discontinuation visit and 120 (±30) days after the last dose of atezolizumab or placebo is still required.

[b] Whole blood, serum, plasma.

[c] Plasma.

Appendix 4
Interim and Final Analyses for Overall Survival

Different Scenarios of PFS and ORR Testing	Alpha Level	Analysis Timing	Time from 1st Patient Enrolled (months)	Information Fraction	No. of Events	Stopping Boundary in HR	Stopping Boundary in p-Value
Both PFS and ORR are statistically significant in both IC1/2/3 and ITT	0.05	First interim	30	53%	IC1/2/3: 133 AC: 347	IC1/2/3: HR ≤ 0.608 AC: HR ≤ 0.735	p-value ≤ 0.0041
		Second interim	41	80%	IC1/2/3: 201 AC: 524	IC1/2/3: HR ≤ 0.726 AC: HR ≤ 0.820	p-value ≤ 0.0231
		Final	56	100%	IC1/2/3: 251 AC: 655	IC1/2/3: HR ≤ 0.774 AC: HR ≤ 0.853	p-value ≤ 0.0425
PFS is statistically significant in both IC1/2/3 and ITT; ORR is statistically significant in either IC1/2/3 or ITT, but not both	0.049	First interim	30	53%	IC1/2/3: 134 AC: 349	IC1/2/3: HR ≤ 0.608 AC: HR ≤ 0.735	p-value ≤ 0.004
		Second interim	41	80%	IC1/2/3: 202 AC: 526	IC1/2/3: HR ≤ 0.725 AC: HR ≤ 0.820	p-value ≤ 0.0225
		Final	56	100%	IC1/2/3: 253 AC: 658	IC1/2/3: HR ≤ 0.774 AC: HR ≤ 0.853	p-value ≤ 0.0417
PFS is statistically significant in both IC1/2/3 and ITT; ORR is not statistically significant in either IC1/2/3 or ITT	0.048	First interim	30	53%	IC1/2/3: 135 AC: 351	IC1/2/3: HR ≤ 0.609 AC: HR ≤ 0.735	p-value ≤ 0.0039
		Second interim	42	80%	IC1/2/3: 203 AC: 530	IC1/2/3: HR ≤ 0.725 AC: HR ≤ 0.820	p-value ≤ 0.0210
		Final	57	100%	IC1/2/3: 254 AC: 662	IC1/2/3: HR ≤ 0.774 AC: HR ≤ 0.853	p-value ≤ 0.0408
PFS is statistically significant in either IC1/2/3 or ITT, but not both, and the subsequent ORR is statistically significant	0.045	First interim	30	52%	IC1/2/3: 135 AC: 350	IC1/2/3: HR ≤ 0.602 AC: HR ≤ 0.729	p-value ≤ 0.0031
		Second interim	42	80%	IC1/2/3: 207 AC: 538	IC1/2/3: HR ≤ 0.724 AC: HR ≤ 0.819	p-value ≤ 0.0204
		Final	59	100%	IC1/2/3: 259 AC: 673	IC1/2/3: HR ≤ 0.773 AC: HR ≤ 0.852	p-value ≤ 0.0384

Appendix 4
Interim and Final Analyses for Overall Survival (cont.)

Different Scenarios of PFS and ORR Testing	Alpha Level	Analysis Timing	Time from 1st Patient Enrolled (months)	Information Fraction	No. of Events	Stopping Boundary in HR	Stopping Boundary in p-Value
PFS is statistically significant in either IC1/2/3 or ITT, but not both ; ORR is not statistically significant	0.044	First interim	30	52%	IC1/2/3: 136 AC: 352	IC1/2/3: HR ≤ 0.601 AC: HR ≤ 0.729	p-value ≤ 0.003
		Second interim	43	80%	IC1/2/3: 209 AC: 542	IC1/2/3: HR ≤ 0.725 AC: HR ≤ 0.819	p-value ≤ 0.0200
		Final	59	100%	IC1/2/3: 261 AC: 677	IC1/2/3: HR ≤ 0.773 AC: HR ≤ 0.852	p-value ≤ 0.0376
PFS is not statistically significant in either IC1/2/3 or ITT	0.04	First interim	30	50%	IC1/2/3: 134 AC: 347	IC1/2/3: HR ≤ 0.586 AC: HR ≤ 0.718	p-value ≤ 0.002
		Second interim	44	80%	IC1/2/3: 214 AC: 554	IC1/2/3: HR ≤ 0.723 AC: HR ≤ 0.818	p-value ≤ 0.0179
		Final	62	100%	IC1/2/3:268 AC: 693	IC1/2/3: HR ≤ 0.772 AC: HR ≤ 0.851	p-value ≤ 0.0344

HR = Hazard ratio, IC = tumor-infiltrating immune cell, ITT = intent to treat, ORR = objective response rate, PFS = progression-free survival,