Official Title: A Phase III, Multicenter, Randomized, Open-Label Study Comparing Atezolizumab (Anti-Pd-L1 Antibody) in Combination With Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone in Patients With Operable Triple-Negative Breast Cancer

NCT Number: NCT03498716

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY COMPARING ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ADJUVANT ANTHRACYCLINE/TAXANE-BASED CHEMOTHEREAPY VERSUS CHEMOTHERAPY ALONE IN PATIENTS WITH OPERABLE TRIPLE NEGATIVE BREAST CANCER**

STUDY NUMBER:	BIG 16-05/AFT-27/WO39391
STUDY NAME:	IMpassion030
VERSION NUMBER:	3
ROCHE COMPOUND(S):	Atezolizumab (RO5541267)
EUDRACT NUMBER:	2016-003695-47
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PLAN PREPARED BY:	[redacted] (Roche) [redacted] (FS)

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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DATE FINAL:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statisical Analysis Plan (SAP) was developed based on Roche SAP Legacy model document.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
3	see electronic date stamp on the last page of this document	V 9, approval pending
2	6 September 2022	V 8, 24 November 2021
1	16 March 2020	V 6, 14 February 2020

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This SAP BIG 16-05/AFT-27/WO39391 has been amended to update the interim analyses and provide additional clarifications.

- Based on the U.S. Food and Drug Administration (FDA)'s request, the planned efficacy analyses have been updated and a futility analysis has been added, as described in the corresponding Sections 2.3, 2.4, 3.1, 4.10.1, and 4.10.2 of the SAP. The updated efficacy and futility analyses are based on the actual number of patients randomized at the time of this SAP amendment.
- Additional minor changes have been made to improve clarity and consistency. Table titles have also been added.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody, also known as anti-therapeutic antibody
CCOD	clinical cut-off date
CI	confidence interval
CSR	Clinical Study Report
DFS	disease-free survival
DRFI	distant recurrence-free interval
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5-Dimension, 5-Level
FACT-G	Functional Assessment of Cancer Therapy-General
FWER	familywise error rate
FPI	first patient in
G-CSF	granulocyte colony-stimulating factor
GHS/QoL	global health status quality of life
GM-CSF	granulocyte-macrophage colony stimulating factor
HR	hazard ratio
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cell
iDFS	invasive disease-free survival
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
ISC	Independent Statistical Center
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice or Web-based response system
LS Mean	least squares mean
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NPT	non-protocol therapy
OS	overall survival

PCR	polymerase chain reaction
PD-L1	programmed death ligand-1
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-C30	Quality of Life Questionnaire Core 30
QW	weekly
RFI	recurrence-free interval
SAP	Statistical Analysis Plan
T-AC/EC	atezolizumab and paclitaxel followed by atezolizumab, dose dense doxorubicin or epirubicin
TIL	tumor-infiltrating lymphocytes
TNBC	triple-negative breast cancer

1. BACKGROUND

Study BIG 16-05/AFT-27/WO39391 (also known as ALEXANDRA/IMpassion030) is a global Phase III, open-label, randomized, controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of adjuvant treatment with atezolizumab and paclitaxel followed by atezolizumab, dose dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (referred to as atezolizumab + T-AC/EC) compared with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (referred to as T-AC/EC) in patients with newly diagnosed Stage II-III triple-negative breast cancer (TNBC) who have completed surgery with curative intent of their primary tumor and are candidates for adjuvant systemic therapy following surgery.

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

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 or the Study Schema in Appendix 3.

2.2 ENDPOINTS

See the Protocol Synopsis in Appendix 1 for a description of the endpoints.

2.3 ANALYSIS TIMING

Two interim efficacy analyses for the primary endpoint of invasive disease-free survival (iDFS) will be performed, the first at a time-based cut-off (clinical cut-off date [CCOD[) in February 2023) following a SAP amendment (version 3) and the second at approximately 80% of the total planned number of iDFS events. On the basis of the assumptions presented in Section 2.4 and the number of randomized patients and event accrual information at the time of the SAP amendment (version 3), it is projected that approximately 62% of the iDFS events (242) are observed at the first interim analysis. The 80% of the iDFS events (312) required for the second interim analysis is projected to be observed approximately 10 months (December 2023) after the CCOD of the first interim analysis.

The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary. For example, if exactly 242 events contribute to the first interim analysis, statistical significance will be declared if the p-value from the two-sided stratified log-rank test is ≤ 0.0088 (observed hazard ratio [HR] ≤ 0.71); if the null hypothesis for iDFS is not rejected at the first interim analysis and exactly 312 events contribute to the second interim analysis, statistical significance will be declared if the p-value from the two-sided stratified log-rank test

is ≤0.0218 (observed HR ≤0.77). The applied stopping efficacy boundaries will depend on the actual observed number of events at the time of each analysis. If the null hypothesis for iDFS is not rejected at the interim analyses and the study continues, the final analysis of iDFS will be performed when approximately 390 iDFS events have occurred; statistical significance will be declared if the p-value from the two-sided stratified log-rank test is ≤0.0422 (observed HR ≤0.81), if exactly 390 iDFS events contribute to the final analysis.

At the time of the first interim analysis, a futility analysis will also be conducted. A non-binding futility boundary is set at the iDFS HR of 1, thus futility can be declared if the observed iDFS HR is greater than 1 at the futility analysis. Based on simulations, the probability of crossing the futility boundary is about 10.5% when the underlying iDFS HR is 0.85, and is about 1.2% when the underlying iDFS HR is 0.75, as shown in Table 1.

Table 1 Interim and Final Analyses of the Primary iDFS

Analysis	Number of iDFS Events	Percent Information	Adjusted Two-Sided Alpha Level	Cumulative Power*
iDFS First Interim	242	62%	0.0088	35%
iDFS Second Interim	312	80%	0.0218	61%
iDFS Final	390	100%	0.0422	80%

iDFS = invasive disease-free survival
*For a HR of 0.75 for iDFS

Note: In addition to the scheduled interim analyses the Sponsor may choose to conduct one additional interim efficacy analysis after at least 80% (but less than 100%) of the total planned number of iDFS events have occurred for the primary endpoint of iDFS, after endorsement by the Steering Committee. The decision to conduct an additional interim analysis will be documented in a SAP amendment which will be submitted to the relevant health authorities at least 2 months prior to the conduct of the interim analysis, see Section 4.10.3 for details.

Overall survival (OS) will also be analyzed at the interim and primary (final) analyses of iDFS. Testing on OS will be conducted hierarchically following the sequence defined in Section 4.4.2.

Based on predicted timing and results of the iDFS interim and primary analyses, OS interim and final analyses alpha level and percent information might vary. Predictions for OS are based on protocol assumption. The interim analyses boundaries for statistical significance for OS will be determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary, see Section 4.10.1 for the details.

2.4 DETERMINATION OF SAMPLE SIZE

The final analysis of the primary endpoint of iDFS will take place when approximately 390 iDFS events have occurred in the intent-to-treat (ITT) population (approximately 17% of the planned enrollment of 2300 patients experiencing an iDFS event). At the time of the SAP amendment version 3, 2199 patients have been randomized. The sample size is computed on the basis of the following assumptions:

- Primary statistical test: two-sided, stratified log-rank test at the 0.05 significance level in the ITT population
- Approximately 80% power for iDFS
- A HR of 0.75
- Annual hazard rates of 0.047, 0.108, 0.035, 0.038, 0.029, and 0.014 in Years 1, 2, 3, 4, 5-6, and 7 and thereafter are assumed for the T-AC/EC arm based on the adjuvant TNBC trials: Eastern Cooperative Oncology Group (ECOG) (E1199 [Sparano et al. 2015], BEATRICE [Cameron et al. 2013], and IBCSG 22-00 [Colleoni et al. 2016]).
- Based on the piecewise hazard rates given above for the control arm, and the assumed HR of 0.75 (thus reducing the risk of an iDFS event by 25% at each piecewise interval), the 3-year iDFS rate (probability of not having any iDFS event in the first 3 years) will be 82.7% in the T-AC/EC arm and 86.7% in the atezolizumab + T-AC/EC arm.
- 2.5% annual loss to follow-up for iDFS
- Two interim analyses for iDFS in the ITT population at approximately 62% and 80% of the iDFS, respectively
- One futility analysis for iDFS in the ITT population at the same time as the first interim analysis

Accrual to-date has occurred over 52 months. Based on the current number of enrolled patients, the required number of iDFS events in the ITT population for the final analysis is projected to occur approximately 77 months after first patient in (FPI). Also on the basis of these assumptions, an observed HR of 0.81 or better will result in a statistically significant difference between the treatment arms (i.e., HR = 0.81 will be the minimally detectable difference for the analysis; this corresponds to an improvement in 3-year iDFS from 82.7% in the T-AC/EC arm to 85.7% in the atezolizumab + T-AC/EC arm).

The study duration for the secondary endpoint, OS, was determined on the basis of the number of events required to demonstrate efficacy with regard to OS. A total of approximately 299 deaths are required to achieve 80% power at a two-sided alpha level of 5% to detect an HR of 0.72, corresponding to an improvement in 5-year OS rate from 84% in the T-AC/EC arm to 88.2% in the atezolizumab + T-AC/EC arm assuming a constant hazard. An annual loss to follow-up of 2.5% and three interim analyses are assumed. The final analysis of OS is planned to take place approximately 7 years after the first patient has been randomized.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Patients who provide informed consent and are eligible will be randomized in a 1:1 ratio to receive either of the following treatment regimens:

- **Arm A**: Atezolizumab and Chemotherapy

– Atezolizumab: atezolizumab (840 mg) administered via intravenous (IV) every 2 weeks (Q2W) in combination with chemotherapy (as described below), followed by atezolizumab maintenance therapy (1200 mg IV infusion every 3 weeks [Q3W]) to complete a total duration of 1 year of atezolizumab treatment from the first administration of atezolizumab.

– Chemotherapy: paclitaxel (80 mg/m^2) administered via IV infusion weekly (QW) for 12 weeks followed by dose-dense doxorubicin (60 mg/m^2) or dose-dense epirubicin (90 mg/m^2) IV (investigator's choice) + cyclophosphamide (600 mg/m^2) IV repeated Q2W for 4 doses.

– Granulocyte colony-stimulating factor (G-CSF; e.g., filgrastim or pegfilgrastim) or granulocyte-macrophage colony stimulating factor (GM-CSF) treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy.

- **Arm B**: Chemotherapy alone

– Paclitaxel (80 mg/m^2) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m^2) or dose-dense epirubicin (90 mg/m^2) IV (investigator's choice) + cyclophosphamide (600 mg/m^2) IV repeated Q2W for 4 doses.

– G-CSF (e.g., filgrastim or pegfilgrastim) or GM-CSF treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy.

The study population will be enriched for patients with node-positive disease such that the final population will contain approximately 50% of patients with node-negative disease.

Randomization will be stratified by the following factors:

- Axillary nodal status (0 vs. 1-3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs. mastectomy)
- Tumor programmed death ligand-1 (PD-L1) status (tumor-infiltrating immune cell [IC] 0 vs. IC1/2/3)

Randomization should occur no more than 8 weeks (56 days) after definitive surgery, and study drug administration should begin within 1 week (7 days) after randomization, but no sooner than 2 weeks (14 days) after last surgery.

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will evaluate safety and efficacy data during the study. The iDMC will follow the iDMC charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed by the iDMC on a periodic basis. The first safety review will occur when 50 patients in each treatment arm have received at least 2 doses of doxorubicin/epirubicin and cyclophosphamide (with or without atezolizumab respectively) and the relevant data has been entered in the electronic Case Report Form (eCRF). Subsequent safety reviews will occur at least once every 6 months during the study until the last patient has completed or discontinued study treatment.

Unblinded efficacy data will be reviewed by the iDMC as part of the interim analyses, described in Section 2.3. A planned futility analysis will also be conducted by the iDMC at the time of the first interim analysis. All summaries and analyses for the iDMC review will be prepared by the Independent Statistical Center (ISC).

After reviewing the data, the iDMC will make a recommendation to the Interface Committee as described in the Interface Committee Charter and the iDMC Charter. Final decisions will rest with the Steering Committee.

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 POPUTLATIONS

4.1.1 Randomized Population – Intent-to-Treat (ITT)

The primary analysis population for efficacy is the ITT population, defined as all randomized patients, whether or not the assigned study treatment was received. Patients will be assigned to the treatment group to which they were randomized.

4.1.2 PD-L1−Selected Tumor Status (IC1/2/3) Subpopulation

The PD-L1−selected tumor status (IC1/2/3) subpopulation is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.

4.1.3 Node-Positive Disease Subpopulation

The node-positive disease subpopulation is defined as patients in the ITT population with node-positive disease as defined in the breast cancer history in the clinical database at the time of randomization.

4.1.4 Pharmacokinetic-Evaluable Population

Pharmacokinetic (PK)-evaluable population: all patients who received atezolizumab administration and have at least one evaluable post-baseline PK sample.

4.1.5 Safety Population

The primary analysis population for safety is the safety-evaluable population, defined as all patients who received at least one dose of study medication. Patients will be assigned to treatment groups as treated, and all patients who received at least one dose of atezolizumab will be included in the atezolizumab treatment group.

4.1.6 Immunogenicity Populations

The pretreatment immunogenicity population includes patients who have a pretreatment anti-drug antibody (ADA, also known as anti-therapeutic antibody) assessment. The post-baseline immunogenicity population includes patients with at least one post-baseline ADA assessment and who received at least one dose of atezolizumab. For both populations, patients are grouped according to treatment received.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and discontinuation from the study will be summarized by treatment arm for all randomized patients. The reasons for study discontinuation will be tabulated.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (in particular, stratification variables and ECOG status) will be summarized by treatment arm for all randomized patients. Continuous variables will be summarized with use of means, standard deviations, medians, ranges, and inter-quartile ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

4.4 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will include all randomized patients unless otherwise stated with patients grouped according to their assigned treatment (ITT population).

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is iDFS, defined as the time between randomization and date of first occurrence of an iDFS event, as described in the Protocol Synopsis in Appendix 1. Data from patients who have not had an event at the time of data analysis will be censored on the date on which they are last known to be alive and event free, on or before the clinical data cutoff date of the respective analysis. Patients with no post-baseline information will be censored on the date of randomization plus one day.

The log-rank test, stratified by the protocol-defined stratification factors (as per the interactive voice or Web-based response system [IxRS] system), will be used to

compare iDFS between the two treatment arms. The HR for iDFS will be estimated with use of a stratified Cox proportional hazards model. Stratification factors are defined using IxRS data. The Kaplan-Meier approach will be used to estimate the 3-year iDFS rates, and corresponding 95% confidence intervals (CI), calculated using Greenwood method, for each treatment arm which will be used to describe iDFS in addition to the HR. In addition to the 3-year iDFS rate estimates for other time-points (e.g., 4-year, 5-year) may be evaluated to better characterize the data, if the median follow-up based on the inverse censoring method of the iDFS distribution indicates sufficient support for estimates at timepoints beyond 3 years. The difference between the two treatment arms and corresponding 95% CI will also be calculated.

4.4.2 Key Secondary Efficacy Endpoints

To adjust for multiple statistical testing of the key secondary efficacy endpoints, thereby controlling the overall type I error rate at a two-sided significance level of 5%, the fixed sequence testing procedure will be used (where each subsequent hypothesis will be tested only if all previously tested hypotheses have been rejected). These endpoints will be tested using hierarchical group-sequential testing with separate error spending functions at a two-sided significance level of 0.05 (see Section 4.10) in the following order:

- iDFS in the subpopulation with PD-L1 – selected tumor status (IC1/2/3)
- iDFS in the subpopulation with node-positive disease
- OS
- iDFS, including second primary non-breast invasive cancer (except for non-melanoma skin cancers and in situ carcinoma of any site) as an iDFS event
- Recurrence-free interval (RFI)
- Distant recurrence-free interval (DRFI)
- Disease-free survival (DFS)

The testing hierarchy will place the primary endpoint, iDFS in the ITT population, at the top of the hierarchy (i.e., no alpha-splitting between iDFS and any other endpoint[s]).

4.4.2.1 iDFS in the Subpopulation with PD-L1 – Selected Tumor Status (IC1/2/3)

iDFS is defined in an analogous manner to the primary endpoint, see Section 4.4.1, and will be analyzed with the same methodology in the subpopulation of patients with PD-L1-selected tumor status (IC1/2/3), see Section 4.1.2. The stratification factors used in the analysis are axillary nodal status and surgery as per IxRS.

4.4.2.2 iDFS in the Subpopulation with Node-Positive Disease

iDFS is defined in an analogous manner to the primary endpoint see Section 4.4.1, and will be analyzed with the same methodology in the subpopulation of patients with node-positive disease, see Section 4.1.3.

4.4.2.3 Overall Survival

OS is defined as the time from randomization to the date of death due to any cause. Patients who are not reported as having died at the time of the clinical data cutoff date will be censored at the date when they were last known to be alive. Patients with no post-baseline information will be censored on the date of randomization plus one day. OS will be analyzed with the use of the same methodology as specified for the primary endpoint, see Section 4.4.1.

4.4.2.4 iDFS Including Second Primary Non-Breast Cancer

iDFS is defined in an analogous manner to the primary endpoint, see Section 4.4.1, with the addition of second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) and will be analyzed with the same methodology.

4.4.2.5 Recurrence-Free Interval

RFI is defined as the time from randomization to the first occurrence of any recurrence (local, regional [including invasive ipsilateral tumor and invasive locoregional tumor], or distant), as determined by the investigators.

Patients without an event at the time of clinical cutoff for the analysis will be censored at the last date the patient was known to be alive and event free. Patients without an event who died will be censored at the date of death. Patients with no post-baseline information will be censored on the date of randomization. RFI will be analyzed with the same methodology as specified for the primary endpoint see Section 4.4.1.

4.4.2.6 Distant Recurrence-Free Interval

DRFI is defined as the time from randomization to distant breast cancer recurrence. The censored data will be handled in the same way as RFI, see Section 4.4.2.5. DRFI will be analyzed with the same method as the primary endpoint, see Section 4.4.1.

4.4.2.7 Disease-Free Survival

DFS is defined as the time from randomization until the date of the first occurrence of one of the following events:

- Any of the events specified as per primary endpoint (iDFS), see the Protocol Synopsis in Appendix 1
- New diagnosis of an ipsilateral or contralateral non-invasive breast cancer

DFS will be analyzed with the use of the same methodology as specified for iDFS and will follow similar censoring rules, see Section 4.4.1.

4.4.3 Supportive Secondary Endpoints

The following endpoints are secondary endpoints, however they are not included in the fixed sequence testing procedures. These include patient-reported outcomes (PROs) of

function (role, physical) and health-related quality of life (HRQoL) which are also described in the Protocol Synopsis in Appendix 1.

4.4.3.1 Patient-Reported Outcomes of Role and Physical Function and HRQoL

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (Version 3) 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 using the ITT population.

The primary PRO endpoints are the mean and mean changes from the baseline score in the following scales of the EORTC QLQ-C30: function (role [Q6, Q7], physical [Q1-Q5]) and global health status quality of life (GHS/QoL) (Q29, Q30). These will be analyzed in the ITT population, see Section 4.1.4. Summary statistics (mean [and 95% CI], standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline (and 95% CI) will be calculated and reported for interval and continuous variables. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and GHS/QoL scales (Osoba et al. 1998; Cocks et al. 2011).

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

In case of repeated assessments, the latest assessment will be used in the analysis described above and in summary tables, although all values will be listed.

4.4.4 Exploratory Efficacy Endpoints

4.4.4.1 Patient-Reported Outcomes of Disease/Treatment-Related Symptoms, Emotional and Social Function-EORTC Data

Summary statistics (mean [and 95% CI], standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for all disease/treatment-related symptom items and scales, and the emotional, social function scales of the EORTC QLQ-C30 at each assessment time-point for each arm. These will be analyzed in the ITT population, see Section 4.1.1.

Repeated assessments will be dealt with as described in Section 4.4.3.1.

4.4.4.2 FACT-G, GP5 Single Item Data

A descriptive analysis of absolute scores and the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported for item GP5 ("I am bothered by side effects of treatment") from the Functional Assessment of Cancer Therapy-General (FACT-G) physical well-being subscale. Mean change from baseline scores will also be summarized at each assessment time point by treatment arm as well as graphical representation of FACT-G GP5 data over time will also be provided and summarized over time. Item GP5 from Version 4 of the FACT-G questionnaire will be scored according to the FACIT scoring manual (Cella 1997), and data will be analyzed in the ITT population, see Section 4.1.1.

Repeated assessments will be dealt with as described in Section 4.4.4.1.

4.4.4.3 Health Economic EQ-5D-5L Data

Health utility data from the EuroQoL 5-Dimension, 5-Level (EQ-5D-5L) will be evaluated in pharmacoeconomic models. The results from the health economic data analyses will be reported separately from the CSR.

4.4.5 Sensitivity Analyses

The impact of non-protocol therapy (NPT) on the primary endpoint (iDFS) will be evaluated. NPT is defined as any anti-cancer therapy other than study treatment that typically is the subsequent line of therapy. A sensitivity analysis will be performed in which data for patients who received NPT, prior to an iDFS event, will be censored at the last disease status assessment date on or before the patient received NPT.

The impact of misclassification in the patient's stratification factors of patients on the primary endpoint (iDFS) analysis will be evaluated. A sensitivity analysis will be performed by using the stratification factors based on the eCRF values for axillary nodal status and surgery. This sensitivity analysis will only be run if the observed number of misclassified stratification factors is greater than 10% between the eCRF data and IxRS data. Note that PD-L1 status is only collected in the IxRS system.

The impact of the major escalation of the Ukraine-Russia conflict since 24 February 2022 on the primary analysis of iDFS will be assessed via the following sensitivity analysis: A sensitivity analysis will be performed where data for the patients from Ukraine and Russia whose date of iDFS event or censoring was later than the start date of the conflict, 24 Feb 2022, will be censored at this date.

Additional sensitivity analyses may be considered if appropriate.

4.4.6 Subgroup Analyses

Besides the subgroup analyses of iDFS (subpopulations) mentioned in Section 4.4.2 and Section 4.4.5 , to assess the consistency of the study results across subgroups, iDFS and OS will be evaluated in subgroups defined by:

- PD-L1 status
- Node status (as defined in Section 4.1.3)
- Demographic and relevant baseline characteristics (including geographical region)

Summaries of iDFS and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the 3-year iDFS rates, will be produced separately for each level of the categorical variables. Forest plots will be used to summarize the results. No formal hypotheses testing will be carried out in subgroups, other than those included in Section 4.4.2.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Serum concentrations of atezolizumab will be reported as individual values and descriptive group statistics on the PK-evaluable population (Section 4.1.5). Serum concentrations of atezolizumab over time will be plotted as individual and as mean concentrations. Serum atezolizumab concentrations by treatment-emergent ADA status will be evaluated.

4.6 SAFETY ANALYSES

The safety analyses will be done for the safety-evaluable population defined in Section 4.1.5.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in left ventricular ejection fraction (LVEF), changes in vital signs, and study treatment exposures and will be presented by treatment arm.

4.6.1 Exposure of Study Medication

Study treatment 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 for each study treatment. A summary table reporting treatment with alternative taxanes will also be produced.

4.6.2 Adverse Events

Verbatim descriptions of adverse events will be summarized by mapped term Medical Dictionary for Regulatory Activities (MedDRA), appropriate thesaurus level, and toxicity grade (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0 [v5]). For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately: adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, serious adverse events, adverse events by intensity/severity, Grade 3-4 adverse events, adverse events leading to death and adverse events of special interest for atezolizumab.

All deaths and causes of death will be summarized.

4.6.3 Laboratory Data

Relevant laboratory values will be summarized by time, with NCI-CTCAE v5.0 Grade 3 and Grade 4 values identified, where appropriate. Clinically relevant shifts from baseline (defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post-baseline) will be tabulated by treatment arm.

4.6.4 Vital Signs and ECOG Performance Status

For vital signs, baseline values will be summarized by treatment arm. A table of clinically significant abnormal values by time and by treatment arm will also be presented. Change from baseline in selected vital signs will be summarized by treatment arm.

ECOG values (including values collected during the study) will be listed.

4.6.5 ECG

For ECG, baseline values will be summarized by treatment arm and results of on-study ECGs (done when clinically indicated) will be listed.

4.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include all patients in the immunogenicity population, see Section 4.1.6.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized.

When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, and pharmacokinetics may be investigated.

4.8 BIOMARKER ANALYSES

The primary endpoint (iDFS) will be assessed in the subpopulation of patients with PD-L1-selected tumor status (IC1/2/3) as a secondary endpoint, see Section 4.4.2.1. Exploratory biomarker analyses will be performed in baseline pretreatment, on-treatment, follow-up and recurrence samples in an effort to understand the association of these markers with study treatment outcome, including efficacy and/or adverse events. The biomarkers may include, but will not be limited to, PD-L1, stromal tumor-infiltrating lymphocytes (TILs), and other biomarkers in tumor and blood, as defined by immunohistochemistry (IHC), quantitative reverse transcription polymerase chain reaction (PCR), next-generation sequencing (NGS,) or other methods.

4.9 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.

4.10 INTERIM ANALYSES

The interim analyses on the primary endpoint (iDFS) will be conducted by an independent statistical group (ISC) and reviewed by the iDMC. The Sponsor will remain blinded to the results of interim analyses until the unblinding of the study. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter.

To account for the statistical testing of primary and key secondary endpoints at multiple timepoints, hierarchical group-sequential testing with separate error spending functions at level 0.05 (two-sided) will be used. This protects the familywise error rate (FWER) strongly at level 0.05, provided that the testing of each endpoint follows the sequence testing procedure defined in Section 4.4.2. We will use the overall hierarchical principle, where if the primary endpoint is significant at the interim analysis, then the trial continues and the secondary endpoints will be tested at the interim analysis and again at further analyses, if not significant before (Glimm et al. 2009). With this testing strategy, if the primary endpoint (iDFS in the ITT population) is found to be significant at the interim analysis, according to the O'Brien-Fleming boundaries with a Lan-DeMets alpha spending function as defined in Section 4.10.1, then the secondary efficacy endpoints will be tested in the order specified in Section 4.4.2 if, and only if, the preceding null hypothesis in the specified hierarchical order was rejected. With this approach, the overall alpha level is controlled at 0.05 (two-sided), since FWER will be held at 0.05, if this is true for each of the secondary hypotheses tested within the pre-specified group-sequential design.

Note that all the secondary endpoints included in the hierarchical testing with the exception of OS, see Section 4.4.2, will be tested using the same boundaries for

statistical significance calculated for the primary endpoint, see Section 4.10.1. The interim analyses boundaries for statistical significance of key secondary endpoint OS will also be determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary as defined in Section 4.10.2.

4.10.1 Invasive Disease-Free Survival (Specified)

Two interim efficacy analyses for the primary endpoint of invasive disease-free survival (iDFS) will be performed, the first at a time-based cut-off (clinical cut-off date [CCOD[) in February 2023) following a SAP amendment (version 3) and the second at approximately 80% of the total planned number of iDFS events. On the basis of the assumptions presented in Section 2.4 and the number of randomized patients and event accrual information at the time of the SAP amendment (version 3), it is projected that approximately 62% of the iDFS events (242) are observed at the first interim analysis. The 80% of the iDFS events (312) required for the second interim analysis is projected to be observed approximately 10 months (December 2023) after the CCOD of the first interim analysis.

The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary. For example, if exactly 242 events contribute to the first interim analysis, statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $\leq$0.0088 (observed HR $\leq$0.71); if the null hypothesis for iDFS is not rejected at the first interim analysis and exactly 312 events contribute to the second interim analysis, statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $\leq$0.0218 (observed HR $\leq$0.77). The applied stopping boundary will depend on the actually observed number of events. If the null hypothesis for iDFS is not rejected at the interim analyses and the study continues, the final analysis of iDFS will be performed when approximately 390 iDFS events have occurred; statistical significance will be declared if the p-value from the two-sided stratified log-rank test is p $\leq$0.0422 (observed HR $\leq$0.81), if exactly 390 iDFS events contribute to the analysis.

Note that this analysis boundary will also be used to test the secondary endpoints defined in Section 4.4.2, with the exception of OS, for which the analysis boundary is discussed in Section 4.10.2. These are:

- iDFS in the subpopulation with PD-L1-selected tumor status (IC1/2/3)
- iDFS in the subpopulation with node-positive disease
- iDFS, including second primary non-breast invasive cancer (except for nonmelanoma skin cancers and in situ carcinoma of any site) as an iDFS event
- Recurrence-free interval (RFI)
- Distant recurrence-free interval (DRFI)
- Disease-free survival (DFS)

Therefore, it is assumed that the information fraction for each of these endpoints is similar to the information fraction for the primary iDFS endpoint (in the ITT population) at the interim analyses. In other words, it is assumed that around 62% and 80% of the events (for the above endpoints) have occurred at the time of the interim analyses. Adjustment for the actual number of events at the final iDFS analysis will be performed following the method proposed in Wassmer and Brannath (2016).

At the time of the first interim analysis of iDFS, a futility analysis will also be conducted. A non-binding futility boundary is set at the iDFS HR of 1, thus futility can be declared if the observed iDFS HR is greater than 1 at the futility analysis. Based on simulations, the probability of crossing the futility boundary when the underlying iDFS HR is 0.85 is about 10.5%, and when the underlying iDFS HR is 0.75 is about 1.2%.

4.10.2 Overall Survival (Specified)

OS will be analyzed at the interim and final analyses of iDFS, as well as after 299 deaths are observed (OS Final analysis). Testing on OS will be conducted using hierarchical group-sequential testing with separate error spending functions, after iDFS in the ITT population, iDFS in the subpopulation with PD-L1-selected tumor status (IC1/2/3) and iDFS in the subpopulation with node-positive disease are found to be significant, see Section 4.4.2.

The interim analysis boundary for statistical significance for OS will be determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary.

- If the null hypothesis for iDFS is rejected at the first iDFS interim analysis, OS may be tested, for the first time, hierarchically at the time of the first iDFS interim analysis. At this time, it is projected that approximately 132 deaths have occurred and statistical significance will be declared if the p-value from the two-sided stratified log-rank test is ≤ 0.0015 (observed HR ≤ 0.57) depending on the actually observed number of events. If the null hypothesis for OS is not rejected at the first OS interim analysis, OS may be further tested based on the following timings as shown in Table 2.

Table 2 Overall Survival at iDFS First Interim Analysis

Analysis	Number of OS Events	Percent Information	Adjusted Two-Sided Alpha Level	Cumulative Power*
OS First Interim (at the iDFS First Interim)	132	44%	0.0015	10%
OS Second Interim	177	59%	0.0066	30%
OS Third Interim	251	84%	0.0266	66%
OS Final	299	100%	0.0410	80%

iDFS = invasive disease-free survival; OS = overall survival.

*For a HR of 0.72 for OS

- If the null hypothesis for iDFS is not rejected at the first iDFS interim analysis and the study continues, OS may be tested, for the first time, hierarchically at the second iDFS interim analysis. At this time, it is projected that approximately 177 deaths will have occurred and statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $p \leq 0.0070$ (observed HR ≤ 0.67) depending on the actually observed number of events. If the null hypothesis for OS is not rejected at the first OS interim analysis, OS may be further tested based on the following timings as shown in Table 3.

Table 3 Overall Survival at iDFS Second Interim Analysis

Analysis	Number of OS Events	Percent Information	Adjusted Two-Sided Alpha Level	Cumulative Power*
OS First Interim (at the iDFS Second Interim)	177	59%	0.0070	30%
OS Second Interim	251	84%	0.0267	66%
OS Final	299	100%	0.0411	80%

iDFS = invasive disease-free survival; OS = overall survival.
*For a HR of 0.72 for OS

- If the null hypothesis for iDFS is not rejected at the second iDFS interim analysis and the study continues, OS may be tested, for the first time, hierarchically at the time of the final analysis of iDFS. At this time, it is projected that approximately 251 deaths will have occurred and statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $p \leq 0.0289$ (observed HR ≤ 0.76) depending on the actually observed number of events. If the null hypothesis for OS is not rejected at the first OS interim analysis, OS may be further tested based on the following timings as shown in Table 4.

Table 4 Overall Survival at iDFS Final Analysis

Analysis	Number of OS Events	Percent Information	Adjusted Two-Sided Alpha Level	Cumulative Power*
OS First Interim (at the iDFS Final)	251	84%	0.0289	66%
OS Final	299	100%	0.0417	80%

iDFS = invasive disease-free survival; OS = overall survival.
*For a HR of 0.72 for OS

Adjustment for the actual number of events at the final OS analysis may be performed following the method proposed in Wassmer and Brannath (2016). 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.

4.10.3 Invasive Disease-Free Survival (and Overall Survival) (Optional)

To adapt to information that may emerge during the course of this study, in order to ensure patient benefit, the Sponsor may choose to conduct one additional interim efficacy analysis after at least 80% of the total planned number of iDFS events have occurred for the primary endpoint of iDFS. An additional interim efficacy analysis will only be conducted after endorsement by the Steering Committee. The key secondary endpoints defined in Section 4.4.2 would also be tested at this time using hierarchical group-sequential testing with separate error spending functions at level 0.05. Below are the specifications 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 an additional 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 Steering Committee of the study as a result of the analysis (continuation of the study without modifications, continuation of the study with modification(s) for reasons including, but not restricted to, safety concerns and discontinuation or temporary suspension for reasons including, but not restricted to, safety concerns), 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. Specifically, the Lan-DeMets alpha-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). If the study continues beyond the interim analyses, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance.

5. REFERENCES

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Appendix 1 Protocol Synopsis

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY COMPARING ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ADJUVANT ANTHRACYCLINE/TAXANE-BASED CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE IN PATIENTS WITH OPERABLE TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	BIG 16-05/AFT-27/WO39391
VERSION NUMBER:	8
EUDRACT NUMBER:	2016-003695-47
IND NUMBER:	123277
NCT NUMBER:	NCT03498716
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	III
INDICATION:	Triple-negative breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd
ACADEMIC PARTNERS:	Breast International Group (BIG) Alliance Foundation Trials (AFT) Institut Jules Bordet/Clinical Trials Support Unit (IJB/CTSU) Frontier Science Foundation

OBJECTIVES AND ENDPOINTS

This study (Study BIG 16-05/AFT-27/WO39391, also known as ALEXANDRA/IMpassion030) will evaluate the efficacy, safety, and pharmacokinetics of adjuvant atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (referred to as atezolizumab + T-AC/EC) compared with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (referred to as T-AC/EC) in patients with Stage II-III triple-negative breast cancer (TNBC). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with TNBC	• iDFS, defined as the time from randomization until the date of the first occurrence of one of the following events: – Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)

• Objectives	• Corresponding Endpoints
• **Primary Efficacy Objective (cont.):**	
•	– Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast) – Ipsilateral second primary invasive breast cancer – Contralateral invasive breast cancer – Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the sites mentioned above]) that has either been histologically confirmed and/or clinically/radiographically diagnosed as recurrent invasive breast cancer – Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause
Secondary Efficacy Objectives:	
• To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone	• iDFS in the subpopulation with PD-L1-selected tumor status (IC1/2/3) • iDFS in the subpopulation with node-positive disease • OS, defined as the time from randomization to death from any cause • iDFS defined the same way as the primary endpoint but including second primary non-breast invasive cancer (except for non-melanoma skin cancers and in situ carcinoma of any site) as an event • RFI, defined as the time from randomization until local, regional, or distant disease recurrence • Distant RFI, defined as the time from randomization until distant disease recurrence only • DFS, defined as the time from randomization to the first occurrence of disease recurrence or death from any cause. • Events defining DFS: – Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion) – Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)

• Objectives	• Corresponding Endpoints
Secondary Efficacy Objectives (cont.):	
•	– Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the sites mentioned above]) that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer – Contralateral invasive breast cancer – Ipsilateral or contralateral DCIS – Second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) – Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified it at all possible
• To evaluate PROs of function and HRQoL associated with atezolizumab + T-AC/EC compared with T-AC/EC alone, as measured by the functional and HRQoL- scales of the EORTC QLQ-C30	• Mean and mean changes from baseline score in function (role, physical) and GHS/HRQoL by assessment timepoint, and between treatment arms as assessed by the functional and GHS/HRQoL scales of the EORTC QLQ-C30
Exploratory Efficacy Objectives:	
• To evaluate PROs of disease/treatment-related symptoms associated with atezolizumab + T-AC/EC compared with T-AC/EC alone, as measured by the EORTC QLQ-C30	• Mean and mean changes from baseline score in disease/treatment-related symptoms by assessment timepoint, and between treatment arms as assessed by all symptom items/scales of the EORTC QLQ-C30
• To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to T-AC/EC compared with T-AC/EC alone, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical well-being subscale of the FACT-G quality-of-life instrument	• Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G
• To evaluate patient's health utility as measured by the EQ-5D-5L questionnaire to generate utility scores for use in economic models for reimbursement	• Utility scores of the EQ-5D-5L questionnaire
Safety Objective:	
• To evaluate the safety and tolerability of atezolizumab + TAC/EC compared with T-AC/EC alone	• Occurrence and severity of adverse events as defined by NCI CTCAE v5.0
Pharmacokinetic Objective:	
• To characterize the serum pharmacokinetics of atezolizumab when administered in combination with T-AC/EC chemotherapy	• Serum concentration of atezolizumab at specified timepoints

• Objectives	• Corresponding Endpoints
Immunogenicity Objective:	
• To evaluate the immune response to atezolizumab	• Incidence of ADAs during the study relative to the prevalence of ADAs at baseline
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	
• To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in tumor tissue and blood and their association with efficacy endpoints including, but not limited to, disease recurrence	• Relationship between tumor derived RNA-based immune and tumor gene signatures and efficacy endpoints including, but not limited to, the primary endpoint (iDFS) • Relationship between tumor-based TILs and/or CD8 IHC and efficacy endpoints including, but not limited to, the primary endpoint (iDFS)
• To identify biomarkers that are associated with resistance to atezolizumab in combination with T-AC/EC or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue between pretreatment and post-recurrence samples collected at disease recurrence. These biomarkers may include, and are not limited to, the following: – Acquired mutations assessed using DNA NGS – Changes in the tumor immune microenvironment and biology as assessed by RNA profiling and IHC

ADA = anti-drug antibodies; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQoL 5 Dimension, 5 Level; FACT-G = Functional Assessment of Cancer Therapy-General; GHS = global health status; HRQoL = health-related quality of life; IC = tumor-infiltrating immune cell, iDFS = invasive disease-free survival; IHC = immunohistochemistry; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NGS = next-generation sequencing; OS = overall survival; PK = pharmacokinetic; PRO = patient-reported outcomes; QLQ-C30 = Quality of Life Questionnaire-Core 30; RFI = recurrence-free interval; T-AC/EC = paclitaxel, dose-dense doxorubicin/epirubicin, and cyclophosphamide; TILs = tumor-infiltrating lymphocyte; TNBC = triple-negative breast cancer.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a global Phase III, open-label, randomized, controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of adjuvant treatment with atezolizumab + T-AC/EC compared with T AC/EC alone in patients with newly diagnosed TNBC who have completed surgery with curative intent of their primary tumor and are candidates for adjuvant systemic therapy following surgery.

The HER2 and ER/PgR status will be used to define TNBC. The HER2 negativity will be defined by central laboratory assessment using in situ hybridization (ISH) or immunohistochemistry (IHC) assays per the criteria outlined in the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for HER2 testing. ER/PgR negativity will be defined by central laboratory assessment using IHC assays per the criteria outlined in the ASCO/CAP guidelines for ER/PgR testing. Central laboratory assessment will occur prior to randomization. Patients whose tumors are not confirmed to be triple negative by central laboratory assessment will not be eligible. The PD-L1 status will be assessed by central laboratory. Patients whose tumor tissue is not evaluable for PD-L1 will not be eligible. All site and study team staff will be blinded to PD-L1 status.

Patients who provide informed consent and are eligible will be randomized in a 1:1 ratio to receive either of the following treatment regimens:

- **Arm A**: Atezolizumab and Chemotherapy
  - Atezolizumab: atezolizumab (840 mg) administered via IV Q2W in combination with chemotherapy (as described below), followed by atezolizumab maintenance therapy (1200 mg IV infusion every 3 weeks [Q3W]) to complete a total duration of 1 year of atezolizumab treatment from the first administration of atezolizumab.
  - Chemotherapy: paclitaxel (80 mg/m2) administered via IV infusion weekly (QW) for 12 weeks followed by dose-dense doxorubicin (60 mg/m2) or dose-dense epirubicin (90 mg/m2) IV (investigator's choice) + cyclophosphamide (600 mg/m2) IV repeated Q2W for 4 doses.
  - Granulocyte colony-stimulating factor (G-CSF) (e.g., filgrastim or pegfilgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF) treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, European Organisation for Research and Treatment of Cancer (EORTC), or European Society for Medical Oncology (ESMO) guidelines or per local standard practice.
- **Arm B**: Chemotherapy alone
  - Paclitaxel (80 mg/m2) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m2) or dose-dense epirubicin (90 mg/m2) IV (investigator's choice) + cyclophosphamide (600 mg/m2) IV repeated Q2W for 4 doses.
  - Granulocyte colony-stimulating factor (e.g., filgrastim or pegfilgrastim) or GM-CSF treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, EORTC, or ESMO guidelines or per local standard practice.

The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of patients with node-negative disease.

Patients who do not initially meet all eligibility criteria, other than TNBC status, may be re-screened once.

Randomization will be stratified by the following factors:

- Axillary nodal status (0 vs. 1-3 vs. $\geq$4 positive lymph nodes)
- Surgery (breast conserving vs. mastectomy)
- Tumor PD-L1 status (tumor-infiltrating immune cell [IC]0 vs. IC1/2/3)

Randomization should occur no more than 8 weeks (56 days) after definitive surgery, and study drug administration should begin within 1 week (7 days) after randomization but no sooner than 2 weeks (14 days) after last surgery. In case of multiple surgeries performed for the breast cancer treatment, this time period should count starting from the last performed curative surgery.

To ensure comparability of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will undergo similar assessments as patients in Arm A. These assessments will consist of formal clinic visits for evaluation of symptoms and adverse events, including cardiac toxicity. Following the induction period, patients in Arm B will continue PRO assessments, laboratory evaluations, left ventricular ejection fraction (LVEF) monitoring, and limited physical examinations on a regular basis for the first year after randomization. For patients in both arms, patient-reported outcome (PRO) assessments, LVEF monitoring, physical examinations and other assessments will continue at a reduced frequency after the first year after randomization.

Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

In case of unacceptable toxicity attributed to chemotherapy in Arm A, atezolizumab should be stopped and restarted together with chemotherapy if there is no contraindication. In cases where chemotherapy is permanently discontinued, atezolizumab may be restarted if there is no contraindication and should be based on investigator's assessment of benefit–risk. The Medical Monitor is available to advise as needed. In case of toxicities attributed to atezolizumab, chemotherapy may be continued independently of atezolizumab if there is no contraindication. Atezolizumab may be restarted when the conditions for retreatment have been met. When atezolizumab is restarted, the infusions should remain synchronized and aligned with the chemotherapy schedule and it should be administered at a scheduled atezolizumab visit (i.e., missed doses of atezolizumab will not be made up).

Dose delay and modification guidelines for chemotherapy are provided in the protocol. Management guidelines for toxicities associated with atezolizumab are provided in the protocol.

Treatment will be discontinued in the event of disease recurrence, unacceptable toxicity/adverse event occurrence, pregnancy, withdrawal of consent, significant protocol violations, or study termination. Patients who prematurely discontinue from the study will not be replaced. Except for patients who withdraw consent from study follow-up, those who have prematurely discontinued from treatment will be followed for safety (including cardiac toxicity) and efficacy endpoints.

Efficacy, safety, laboratory, PROs, pharmacokinetic (PK) measures, and biomarkers will be assessed throughout the study. Following completion of study treatment, all patients will continue to be followed for efficacy, safety, and PRO objectives until the end of the study.

Safety assessments will include the occurrence and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). The LVEF will be assessed serially by echocardiogram (ECHO)/multiple-gated acquisition (MUGA) scans. 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 plasma and blood, will be collected for exploratory biomarker assessments.

An Independent Data Monitoring Committee (IDMC) will evaluate safety and efficacy data during the study. No IDMC member may participate in the Study as an investigator, co-investigator, sub-investigator, committee member (other than IDMC), or patient, or in any other capacity that might compromise his or her independence and privileged activities within the IDMC. In order to ensure independence, members should have no involvement in the design and conduct of the Study except through their role on the IDMC and have no financial or other interests in the sponsor's business or other Study organizers (BIG, AFT, FS, IJB) that could influence (or be perceived to influence) their objectivity in evaluating Study data. The IDMC will follow a charter that outlines the IDMC roles and responsibilities.

NUMBER OF PATIENTS

Approximately 2300 patients will be enrolled in this study at approximately 370–450 sites globally. It is estimated that the study will enroll patients over approximately 4 years.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability to comply with protocol, in the investigator's judgment
- Women or men aged ≥ 18 years at time of signing ICF
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Non-metastatic operable Stage II-III breast cancer
  - Patients with node-negative disease must have a pathological tumor size > 2 cm. Patients with node-negative multifocal, multicentric- or bilateral breast cancer are eligible providing that at least one lesion is > 2 cm in size.
- Histologically documented TNBC (negative HER2, ER, and PgR status)

- HER2 negativity will be defined by central laboratory assessment using ISH or IHC assays per ASCO/CAP criteria and ER/PgR negativity will be defined by central laboratory assessment using IHC per ASCO/CAP criteria. Central laboratory assessment will occur prior to randomization.
- Patients with multifocal invasive tumors (more than one tumor confined to the same quadrant as the primary tumor) or multicentric invasive tumors (more than one tumor in different quadrants of the same breast) are eligible provided all discrete lesions are sampled and centrally confirmed as TNBC. Patients with non-TNBC invasive components are not eligible to participate in this study.

- Confirmed tumor PD-L1 evaluation as documented through central testing of a representative tumor tissue specimen
- Adequately excised: Patients must have undergone either breast-conserving surgery or mastectomy/nipple- or skin-sparing mastectomy.
  - For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. In cases in which the patient underwent breast-conserving surgery and there was a microscopic positive deep margin (with no other positive margins), if the tumor was resected up to the chest wall muscle and the surgeon considers that a mastectomy will not provide a negative deep margin, the patient does not need to undergo a mastectomy in order to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.
  - For patients who undergo mastectomy/nipple- or skin-sparing mastectomy, margins must be free of gross residual tumor. It is recommended that patients should have a negative microscopic margin in accordance with local pathology protocol. Patients with a microscopic positive deep margin are eligible.
- Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 8th edition): Patient must have had sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND) for evaluation of pathologic nodal status.
  - Axillary nodal dissection(s) should yield a total of at least six nodes (including the axillary lymph nodes resected at the SLNB plus the lymph nodes collected at the axillary nodal dissection).
  - Patients with positive SLNB should undergo axillary dissection unless all of the following characteristics apply:

    No palpable nodes

    No more than 2 pathologically positive lymph nodes

    Breast-conserving surgery has been completed with tangential whole breast irradiation planned OR mastectomy with regional nodal radiotherapy planned.

    Clinical tumor size $\leq$ T2 (5 cm)
  - In the case that all of the above are applicable, it is not mandatory to have the axillary dissection but it is left at the discretion of the investigator as per site standard practice.
  - In the case of subjects with tumors >2cm and regional lymph node found to have micrometastases or isolated tumor cells: Pathological classification of regional lymph node micrometastases (tumor deposits $>$ 0.2 mm and $\leq$ 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0.

    The study population will be enriched for patients with node-positive disease such that the final population will contain at least 50% node-positive patients.

- Patients with synchronous bilateral invasive disease are eligible only if all bilateral invasive lesions are histologically confirmed as triple negative by central laboratory and have completed adequate pathological tumor-node metastasis staging bilaterally as described above.
- No more than 8 weeks (56 days) may elapse between definitive breast surgery (or the last surgery with curative intent if additional resection is required for breast cancer) and randomization.
- Baseline LVEF ≥ 53% measured by ECHO (preferred) or MUGA scans
  - Baseline LVEF to be conducted within 28 days prior to randomization.
- Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 28 days prior to randomization:
  - Absolute neutrophil count (ANC) ≥ 1500 cells/μL (without G-CSF support within 2 weeks prior to Cycle 1, Day 1)
  - Lymphocyte count ≥ 500 cells/μL
  - Platelet count ≥ 100,000 cells/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - AST, ALT, and alkaline phosphatase ≤ 2.5 × the upper limit of normal (ULN)
  - Serum total bilirubin ≤ 1.0 × ULN

    Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
  - For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN within 28 days prior to randomization
  - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding randomization
  - Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin ≥ 2.5 g/dL
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total 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 total HBcAb test.
- 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.
- Representative formalin-fixed, paraffin embedded (FFPE) tumor specimen from surgical resection in paraffin blocks (preferred) or approximately 25 unstained slides (minimum of 20 slides), with an associated pathology report documenting locally assessed ER, PgR, and HER2 negativity.
  - Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated centrally for PD-L1 expression prior to enrollment. Fine-needle aspiration, brushing, cell pellet from cytology specimens are not acceptable. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible.
  - If multiple tumor specimens are submitted, 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.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, or 6 months after the last dose of paclitaxel or doxorubicin/epirubicin, or 12 months after the last dose of cyclophosphamide, whichever is later. Women must refrain from donating eggs during the same period.
  - 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 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, and copper intrauterine devices.
  - 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 adequate 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, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of paclitaxel, or doxorubicin/epirubicin or 12 months after the last dose of cyclophosphamide, whichever is later. Men must refrain from donating sperm during this same period.
  - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of paclitaxel, or doxorubicin/epirubicin or 12 months after the last dose of cyclophosphamide, whichever is later to avoid exposing the embryo.
  - 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 postovulation methods) and withdrawal are not adequate methods of contraception.
- Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) and have not undergone a sterilization procedure must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires

Exclusion Criteria

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

- Prior history of invasive breast cancer
- Any T4 tumor as defined by tumor-node metastasis classification in UICC/AJCC, 8th edition, including inflammatory breast cancer
- For the currently diagnosed breast cancer, any previous systemic anti-cancer treatment (e.g., neoadjuvant or adjuvant), including, but not limited to, chemotherapy, anti-HER2 therapy (e.g., trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib, or other tyrosine kinase inhibitors), hormonal therapy, or anti-cancer RT other than planned in the context of this study
- Previous therapy with anthracyclines or taxanes for any malignancy
- History of DCIS and/or LCIS that was treated with any form of systemic, hormonal therapy, or RT to the ipsilateral breast where invasive cancer subsequently developed

  - Patients who had their DCIS/LCIS treated only with surgery and/or contralateral DCIS treated with RT are allowed to enter the study.
- Contraindication to RT when adjuvant RT is clinically indicated
- Cardiopulmonary and/or cerebrovascular dysfunction as defined by any of the following prior to randomization
  - History of NCI CTCAE (v5.0) Grade $\geq$ 2 symptomatic congestive heart failure or New York Heart Association (NYHA) Class $\geq$ II
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second degree AV-block Type 2 Mobitz 2, or third-degree AV-block])
  - Significant symptoms (Grade $\geq$ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to randomization
  - Uncontrolled hypertension (systolic blood pressure $>$ 160 mmHg and/or diastolic blood pressure $>$ 100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
  - Cerebrovascular ischemic event (e.g., ischemic within 12 months prior to randomization)
- Prior malignancies 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 (i.e., adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the paclitaxel (e.g., polyoxyl 35 castor oil), cyclophosphamide, or doxorubicin/epirubicin formulations
- Known allergy or hypersensitivity to G-CSF or GM-CSF formulations
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.
  - Patients with controlled Type I diabetes mellitus who are on an insulin regimen may be eligible for this study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all the following conditions are met:

    Rash must cover $<$10% of body surface area.

    Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Current treatment with anti-viral therapy for HBV
- Urinary outflow obstruction
- Active tuberculosis
- Severe infections within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during study treatment
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study or within 5 months after the last dose of atezolizumab
  - Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to initiation of study treatment, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists or immune checkpoint-blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] alpha agents) within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication 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 based on investigator's assessment of benefit–risk. The Medical Monitor is available to advise as needed.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
- Pregnant or lactating, or intending to become pregnant during the study
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease
- Under any legal protection (tutorship/curatorship).

END OF STUDY

The study is planned to end after approximately 298 deaths have been observed for the analysis of OS.

LENGTH OF STUDY

The total duration of the study is expected to be approximately 7 years after the first patient is randomized.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) for this study are atezolizumab, paclitaxel, doxorubicin, epirubicin, and cyclophosphamide.

ATEZOLIZUMAB (ARM A ONLY)

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg Q2W (14 [± 3] days) in combination with T-AC/EC chemotherapy. Upon completion of chemotherapy, atezolizumab will be continued as maintenance therapy at a dose of 1200 mg administered by IV infusion Q3W (21 [± 3] days) to complete 1 year of treatment (i.e., approximately 1 year total duration of atezolizumab therapy from first administration of atezolizumab).

BACKGROUND TREATMENT

Patients will receive paclitaxel (80 mg/m^2) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m^2) or dose-dense epirubicin (90 mg/m^2) IV (investigator's choice) + cyclophosphamide (600 mg/m^2) administered via IV infusion Q2W with G-CSF/GM-CSF support for 4 cycles (i.e., a total of 4 doses of doxorubicin/epirubicin and cyclophosphamide).

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy variable is invasive disease-free survival (iDFS), defined as the time between randomization and date of first occurrence of an iDFS event as described in the protocol. Data from patients who have not had an event at the time of data analysis will be censored on the date on which they are last known to be alive and event free, on or before the clinical data cutoff date of the respective analysis.

Patients with no postbaseline information will be censored on the date of randomization.

The log-rank test, stratified by the protocol-defined stratification factors, will be used to compare iDFS between the two treatment arms. The hazard ratio (HR) for iDFS will be estimated with use of a stratified Cox proportional hazards model. The Kaplan-Meier approach will be used to estimate 3-year iDFS rates, and corresponding 95% Cis for each treatment arm will be used to describe iDFS in addition to the HR.

DETERMINATION OF SAMPLE SIZE

The final analysis of the primary endpoint of iDFS will take place when approximately *390* iDFS events have occurred in the intent-to-treat (ITT) population (approximately *17%* of the planned enrollment of 2300 patients experiencing an iDFS event). This sample size is computed on the basis of the following assumptions:

- Primary statistical test: two-sided, stratified log-rank test at the 0.05 significance level in the ITT population
- Approximately 80% power for iDFS
- A HR of 0.75
- Annual hazard rates of 0.047, 0.108, 0.035, 0.038, 0.029, and 0.014 in Years 1, 2, 3, 4, 5–6, and 7 and thereafter are assumed for the T-AC/EC arm based on the adjuvant TNBC trials ECOG E1199, BEATRICE, and IBCSG 22-00
- Based on the piecewise hazard rates given above for the control arm, and the assumed HR of 0.75 (thus reducing the risk of an iDFS event by 25% at each piecewise interval), the 3 year iDFS rate (probability of not having any iDFS event in the first 3 years) will be 82.7% in the T-AC/EC arm and 86.7% in the atezolizumab + T-AC/EC arm
- 2.5% annual loss to follow-up for iDFS

- Two interim analyses for iDFS in the ITT population (see below)
- One futility analysis for iDFS in the ITT population at the same time of the first interim analysis

Accrual is projected to occur over 51 months. The required number of iDFS events in the ITT population is projected to occur 73 months after first patient in. Also, on the basis of these assumptions, an observed HR of 0.81 or better will result in a statistically significant difference between the treatment arms (i.e., HR$=0.81$ will be the minimally detectable difference for the analysis; this corresponds to an improvement in 3-year iDFS from 82.7% in the T-AC/EC arm to 85.7% in the atezolizumab $+$ T-AC/EC arm).

The study duration for the secondary endpoint, OS, was determined on the basis of the number of events required to demonstrate efficacy with regard to OS. A total of 300 deaths are required to achieve 80% power at a two-sided alpha level of 5% to detect an HR of 0.72, corresponding to an improvement in 5-year OS rate from 84% in the T-AC/EC arm to 88.2% in the atezolizumab $+$ T-AC/EC arm assuming a constant hazard. An annual loss to follow-up of 2.5% and two interim $analyses\ of\ OS$ are assumed. The final analysis of OS is planned to take place approximately 7 years after the first patient has been randomized.

INTERIM ANALYSES

One interim efficacy analysis of iDFS will be performed when approximately 80% of the total planned number of iDFS events have occurred. On the basis of the assumption presented above, it is projected that 80% (310) iDFS events will have been observed approximately 59 months after the first patient randomized.

The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets α-spending function with an O'Brien-Fleming boundary. Statistical significance will be declared if the p-value from the two-sided stratified log-rank test is ≤ 0.0244 (observed HR ≤ 0.77) depending on the actually observed number of events. If the null hypothesis for iDFS is not rejected at the interim analysis and the study continues, the final analysis of iDFS will be performed when approximately 388 iDFS events have occurred; statistical significance will be declared if the p-value from the two-sided stratified log-rank test is p ≤ 0.0429 (observed HR ≤ 0.81).

Appendix 2 Schedule of Assessments

	Screening [a]	Treatment [b]		Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B)	Follow-Up [d]
		Induction (28-day Cycles) (Cycles 1-5; Weeks 1-20)	Arm A: Maintenance Arm B: Monitoring (21-day Cycles) (Cycles 6-16; Weeks 21-53)		
	Days - 28 to - 1	Day 1 of each cycle (± 3 days)	Arm A: Day 1 of each cycle (± 3 days); Arm B: Day 1 of every other cycle (± 7 days)		
Informed consent	x [e]				
Baseline tumor tissue sample submission for HER2, HR, and PDL1 determination and exploratory biomarkers (mandatory)	x [f]				
Demographic data	x				
Medical history and baseline conditions	x				
Disease status assessments [g]		x			x
EORTC QLQ-C30, EQ-5D-5L [h]		x [h] (± 3 days)	Arm A: x [h] (± 3 days) Arm B: x [h] (± 7 days)	x [h] (± 3 days)	x [i]
FACT-G, single item GP5 [h]		x [j] (± 3 days)	Arm A: x [j] (± 3 days) Arm B: x [h] (± 7 days)	x [j] (± 3 days)	x [i]
Vital signs [k]	x	On each infusion day	Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6)	x	

Appendix 2 Schedule of Activities (cont.)

	Screening [a]	Treatment [b]		Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B)	Follow-Up [d]
		Induction (28-day Cycles) (Cycles 1–5; Weeks 1–20)	Arm A: Maintenance Arm B: Monitoring (21-day Cycles) (Cycles 6–16; Weeks 21–53)		
	Days −28 to −1	Day 1 of each cycle (±3 days)	Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days)		
Weight	x	x	Arm A: Day 1 of each cycle		
Height	x				
Complete physical examination [l]	x			x	x [g]
Limited physical examination [m]		x	Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6)		
ECOG Performance Status	x			x	
ECG (12-lead) [n]	x	As clinically indicated			
ECHO/MUGA scan [o]	x [o] (±28 days)	x [o]	x [o] (±14 days)	x [o]	x [o] (±28 days)

Appendix 2 Schedule of Activities (cont.)

	Screening [a]	Treatment [b]		Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B)	Follow−Up [d]
		Induction (28−day Cycles) (Cycles 1−5; Weeks 1−20)	Arm A: Maintenance Arm B: Monitoring (21−day Cycles) (Cycles 6−16; Weeks 21−53)		
	Days − 28 to − 1	Day 1 of each cycle (± 3 days)	Arm A: Day 1 of each cycle (± 3 days); Arm B: Day 1 of every other cycle (± 7 days)		
Hematology [p]	x	On each infusion day	Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6)	x	
Chemistry [q]	x	On each infusion day	Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6)	x	
Menopausal status	x			x	1 year after treatment discontinuation at closest visit
Pregnancy test [r]	x [s]	x [r]	x [r]	x [r]	x [r]
Coagulation (INR, aPTT)	x			x	
TSH, free T3 (or total T3 [t]), free T4	x	x [t]		x	
Viral serology [u]	x				

Appendix 2 Schedule of Activities (cont.)

	Screening [a]	Treatment [b]		Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B)	Follow−Up [d]
		Induction (28−day Cycles) (Cycles 1−5; Weeks 1−20)	Arm A: Maintenance Arm B: Monitoring (21−day Cycles) (Cycles 6−16; Weeks 21−53)		
	Days − 28 to − 1	Day 1 of each cycle (± 3 days)	Arm A: Day 1 of each cycle (± 3 days); Arm B: Day 1 of every other cycle (± 7 days)		
Urinalysis [v]	x	x [w]			
Serum autoantibody sample		See Appendix 2 of the Protocol for detailed schedule.			
Serum PK sample for atezolizumab		See Appendix 2 of the Protocol for detailed schedule (Arm A only).			
Serum ADA sample for atezolizumab		See Appendix 2 of the Protocol for detailed schedule (Arm A only).			
Plasma samples for biomarkers		See Appendix 2 of the Protocol for detailed schedule.			
Blood sample for RPBS (optional) [x]		x			
Radiographic assessments (e.g., CT, MRI, PET)	x [y,z]	As clinically indicated			
Bilateral mammogram/breast MRI	x [y]		x [aa]		x [aa]
Tumor biopsy/tumor tissue at relapse, if clinically feasible		At time of recurrence [bb]			
Concomitant medications [ii]	x [cc]	x	Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6)	x	x [dd]

Appendix 2 Schedule of Activities (cont.)

	Screening [a]	Treatment [b]		Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B)	Follow−Up [d]
		Induction (28−day Cycles) (Cycles 1−5; Weeks 1−20)	Arm A: Maintenance Arm B: Monitoring (21−day Cycles) (Cycles 6−16; Weeks 21−53)		
	Days −28 to −1	Day 1 of each cycle (±3 days)	Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days)		
Adverse events [ee]	x [ee]	x [ee]	Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6)	x	x [ee]
Study treatment administration [ff]		x[ff] (±1 day for weekly paclitaxel)	x [gg]		
Survival follow-up and anti-cancer treatment					x [d,hh]

AC = dose-dense doxorubicin + cyclophosphamide; AC/EC = dose-dense doxorubicin/epirubicin + cyclophosphamide; ADA = anti-drug antibody; CT = computed tomography; EC = dose-dense epirubicin + cyclophosphamide; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQoL 5 Dimension, 5 Level; FACT-G = Functional Assessment of Cancer Therapy−General; FFPE = formalin-fixed paraffin embedded; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hormone receptor; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography; PK = pharmacokinetic; RPBS = Research Project Biological Samples; Q2W = every 2 weeks; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Appendix 2 Schedule of Activities (cont.)

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used; such tests do not need to be repeated for screening.

[b] In the event of treatment delay, study visits should continue as scheduled, if feasible. Patients (both in Arm A and on Arm B) who discontinue study treatment prematurely due to an adverse event should conduct a treatment discontinuation visit and move to the follow-up. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported, including during the follow-up period. Additional tests can be performed, if needed, according to standard medical practice.

[c] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment (Arm A) or within 30 days after the last monitoring visit (Arm B).

[d] The follow-up period begins from the date of treatment phase completion/early termination visit with a duration of up to 7 years from the date of randomization of the first patient. Visit windows are ± 28 days for quarterly, semiannual, and annual assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] After signing of the Informed Consent Form, submission of tumor tissue sample to central laboratory can occur. Tumor tissue, which can be obtained outside the 28-day screening period, 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 approximately 25 unstained slides (minimum of 20 slides) should be provided from the surgical resection specimen. Biomarker samples should not be collected for patients enrolling from China prior to the approval from Human Genetic Resources Administration of China.

[g] Disease status based on all available clinical assessments should be documented from the date of randomization at the following timepoints (± 28 days): every 3 months during study treatment and up to 3 years, every 6 months from 3 to 5 years, and annually thereafter unless a recurrence as defined in Section 4.6.6 of the Protocol has occurred. In addition to physical examinations and mammograms, liver function tests, bone scans, chest X-rays/diagnostic CT, liver imaging, or other radiographic modality may be considered when clinically indicated to exclude metastatic disease and within a timeline as per current local standard of practice. Disease recurrence must be confirmed pathologically if clinically feasible. In cases of disease recurrence diagnosed at any time during the study, patients will be out of the study schedule and will be followed once a year (starting 1 year after first relapse) until end of study for survival, anti-cancer medications, and new relapse events.

Appendix 2 Schedule of Activities (cont.)

[h] All PRO assessments (EORTC QLQ-C30, followed by the FACT-G single item GP5, and then the EQ-5D-5L questionnaires) must be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory results or health record, before administration of study treatment, and/or prior to the performance of any other study assessments that could bias patients' responses. Interview assessment by a member of the clinical staff will be allowed if the patient is not able to complete the measure on her or his own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be completed by patients at baseline (Cycle 1, Day 1) (±3 days); on Cycle 4, Day 1 (±3 days); on Day 1 of every other cycle thereafter until Cycle 16 (Arm A [± 3 days], Arm B [± 7days]); and at the end of treatment/monitoring visit. In case the treatment is interrupted/delayed, the patient should repeat the PRO assessment at the next visit, corresponding to the treatment administration day.

[i] Patients who discontinue the study treatment phase (e.g., Arm A Maintenance and Arm B Monitoring) for any reason will continue to complete the EORTC QLQ-C30, FACT-G single item GP5, and EQ-5D-5L questionnaires in-clinic during the follow-up period at the following timepoints: every 3 months (±28 days) for the first year, every 6 months (±28 days) for Years 2−3, and then annually (±28 days) thereafter.

[j] While on study treatment, all patients will complete the FACT-G, single item GP5 beginning on Cycle 4, Day 1 (±3 days); at Day 1 of every other cycle thereafter until Cycle 16 (Arm A [± 3 days], Arm B [± 7days]); and at the end of treatment/monitoring visit. In case the treatment is interrupted/delayed, the patient should repeat the PRO assessment at the next visit, corresponding to the treatment administration day.

[k] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record vital signs at baseline in the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[l] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Special attention should be paid to cardiovascular symptoms (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs). Record abnormalities observed at baseline in the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Special attention should be paid to cardiovascular symptoms (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[n] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes or as per local practice prior to ECG recording.

[o] Cardiac monitoring (ECHO/MUGA scans) will be performed in all patients enrolled in the study. ECHO is the preferred method. The same method used for a given patient at screening should be used throughout the study.

Appendix 2 Schedule of Activities (cont.)

For both Arms A and B, ECHO/MUGA scans should be obtained at baseline (i.e., screening ECHO/MUGA), between the second dose of AC/EC and the third dose of AC/EC (which should usually occur approximately between Week 16 and Week 18 if no treatment delays), and then every 3 months [i.e., at Week 26 (± 14 days), at Week 39 (± 14 days), and at Week 52 (± 14 days) if no treatment delays]. ECHO/MUGA scans should be obtained at the early termination visit if not performed within the previous 6 weeks. During the survival follow-up period, ECHO/MUGA scans should be obtained annually until the end of study.

During the follow-up period, ECHO/MUGA scans should be obtained annually until the end of study (except for patients who experienced a recurrence of disease).

[p] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[q] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH. Magnesium and phosphorus should be included at screening and as clinically indicated during study treatment. Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms (e.g., abdominal pain, digestive disorders) suggestive of pancreatitis. Bicarbonate/total CO2 should be determined if clinically indicated or considered standard of care.

[r] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at the following specified subsequent visits for women of childbearing potential (including premenopausal women who have had tubal ligation) and women not meeting the definition of postmenopausal: For Arm A at Day 1 of Cycles 1−16, at treatment discontinuation visit, and every 4 weeks until 6 months after treatment discontinuation (last administered dose of study treatment) including for patients who experienced a disease recurrence. For Arm B at Day 1 of Cycles 1−5, at treatment discontinuation visit, and every 4 weeks until 6 months after last administered dose of study treatment including for patients who experienced a disease recurrence. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[s] Screening pregnancy test results must be obtained within 14 days prior to initiation of study treatment.

[t] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter. Patients in Arm B can have thyroid function tests at Cycle 1, Cycle 4, and Cycle 8 and then continue being tested every fourth cycle.

[u] At screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[v] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Appendix 2 Schedule of Activities (cont.)

[w] Urinalysis should be performed as clinically indicated during study treatment.

[x] Not applicable for a site that has not been granted approval for RPBS. Performed only for patients at participating sites who have provided written informed consent to participate. Whole blood for DNA isolation will be collected from patients who have consented to optional RPBS at Week 1, Day 1 (Cycle 1, Day 1). If, however, the RPBS 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.

[y] Within 6 months prior to randomization (except for patients who do not have any remaining breast tissue due to prior prophylactic breast surgery).

[z] Per local standard practice

[aa] Mammograms of any remaining tissue should be performed at least annually (±3 months) from the date of the mammogram performed at screening/surgery and as clinically indicated based on findings from physical examinations.

[bb] Patients are required to undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease relapse. Examples of when tumor biopsy sample collection may be considered not clinically feasible include, but are not limited to, cases where the location of the tumor renders tumor biopsy unsafe or not clinically feasible per the investigator due to patient concerns or is prohibited by the institution or country. Biomarker samples should not be collected for patients enrolling from China prior to the approval from Human Genetic Resources Administration of China.Biopsies should be performed within 40 days after recurrence. An FFPE block or at least 20 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, bone metastases, and lavage samples are not acceptable. For core needle biopsy specimens, at least two cores should be submitted for evaluation. See Section 4.6.7 of the Protocol for tissue sample requirements.

[cc] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit. Record all prior anti-cancer therapies.

[dd] All new anti-cancer treatments are to be reported during the follow-up period.

[ee] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 of the Protocol). 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 treatment or trial-related procedures until a final outcome can be reported.

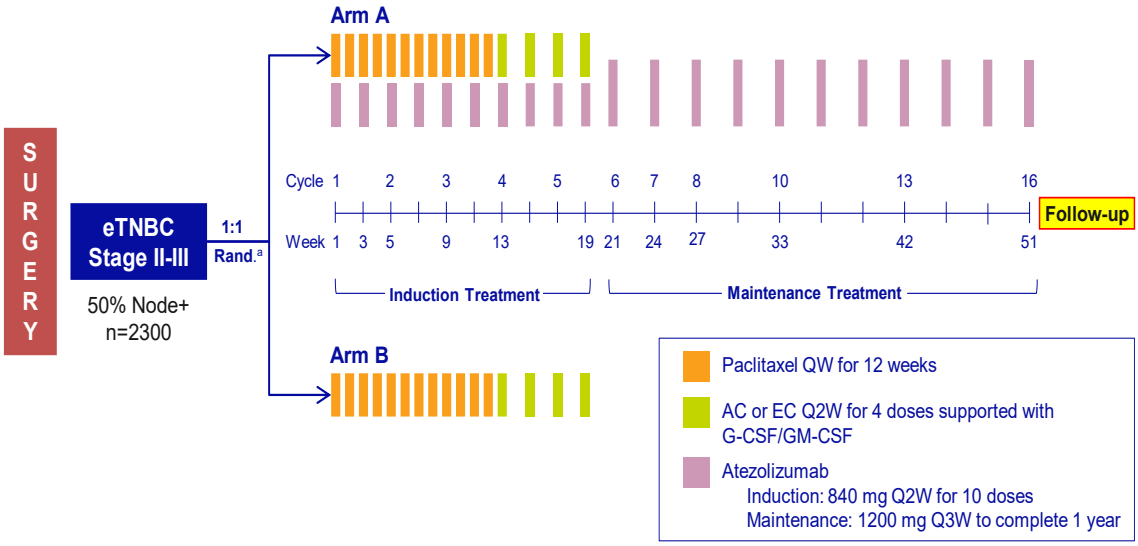
Appendix 2 Schedule of Activities (cont.)

[ff] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Paclitaxel should be administered as an IV infusion QW (7 [± 1] days). During the induction treatment phase, the interval between the end of the weekly paclitaxel (Cycle 3 Visit 4) and the initiation of AC or EC Q2W (Cycle 4 Visit 1) should be 7 days (± 1 day), (i.e., Cycle 4 Visit 1 should be performed at maximum 8 days from Cycle 3 Visit 4, as shown in the study schema [see Figure 1 of the Protocol]). Cyclophosphamide and doxorubicin/epirubicin will be administered Q2W (14 [± 3] days). The 14-days interval only starts after Cycle 4 Visit 1 and the respective ± 3 days window allowed per protocol is only applicable from Cycle 4 Visit 2.

[gg] Study drug administration during the maintenance phase for the atezolizumab-containing arm only

[hh] Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits (unless the patient withdraws consent, or the study is terminated). If a 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 (if allowed per country regulation). Every effort should be made to obtain information on patients who withdraw from the study treatment and/or assessments but have agreed to be contacted for further information (i.e., partial withdrawal). Partial withdrawal from the study, with consent to allow collection of information regarding disease recurrence, survival status, and reportable toxicity should be documented in both the medical records and in the eCRF (i.e., the patient accepted to be contacted for collection of these data despite she/he withdrew consent from the study treatment and/or procedures).

[ii] For patients in Arm B (Monitoring), only medications given for reportable adverse events as per protocol (see Section 5.3.1 of the Protocol) as well as new anti-cancer treatments should be collected.



AC = dose-dense doxorubicin + cyclophosphamide;
EC = dose-dense epirubicin + cyclophosphamide; eTNBC = early triple-negative breast cancer; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; QW = weekly; Q2W = every 2 weeks; Q3W = every 3 weeks; Rand = randomization.

Notes: The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of node-negative patients.
Node-negative patients with tumors ≤ 2 cm in size are not eligible to participate in this study.

G-CSF/pegylated G-CSF/GM-CSF will be used with each dose of AC/EC.

In the induction period, 1 cycle = 4 weeks; in the maintenance period, 1 cycle = 3 weeks.

[a] Randomization should occur no more than 8 weeks after definite surgery, and study drug administration should begin within 1 week after randomization but no sooner than 2 weeks after surgery.

Signature Page for Statistical Analysis Plan - Study WO39391 (IMpassion030) SAP
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Approval Task	[redacted] Company Signatory 28-Feb-2023 21:24:06 GMT+0000