

Official Title: A Phase III, Randomized, Double-Blind, Placebo Controlled Clinical Trial To Evaluate The Efficacy And Safety Of Atezolizumab Or Placebo In Combination With Neoadjuvant Doxorubicin + Cyclophosphamide Followed By Paclitaxel + Trastuzumab + Pertuzumab In Early Her2-Positive Breast Cancer

NCT Number: NCT03726879

Document Date: SAP Version 2: 20 November 2020

STATISTICAL ANALYSIS PLAN

TITLE: A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH NEOADJUVANT DOXORUBICIN + CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL + TRASTUZUMAB + PERTUZUMAB IN EARLY HER2-POSITIVE BREAST CANCER

PROTOCOL NUMBER: BO40747

STUDY DRUG: Atezolizumab

VERSION NUMBER: 2

IND NUMBER: 123277

EUDRACT NUMBER: 2018-001881-40

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [REDACTED]

DATE FINAL: Version 1: 19 November 2019

DATE AMENDED: Version 2: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
20-Nov-2020 13:32:17	Company Signatory	[REDACTED]

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

German(BA) Disease-free survival including contralateral or ipsilateral ductal carcinoma in situ (DCIS) and second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinomas) was added as exploratory efficacy endpoint.

Minor changes have been made to the covariates of the subgroup analyses.

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

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1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the analyses planned to be performed for Study BO40747 (IMpassion050). In relation to the China extension patients, a high-level overview of plans for the China subgroup analyses is provided.

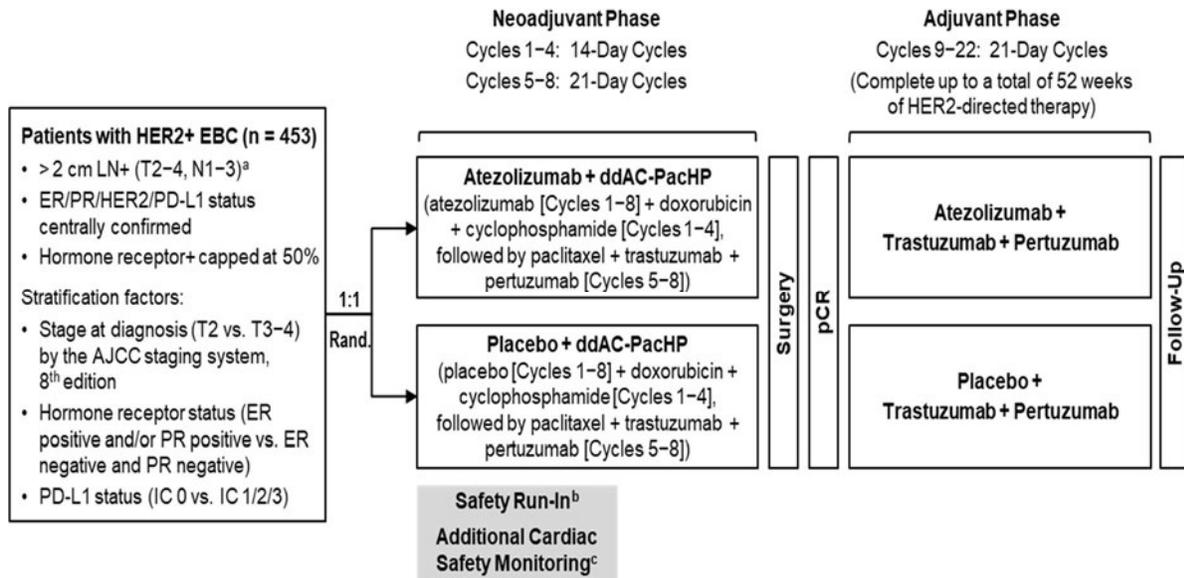
2. STUDY DESIGN

Study BO40747 (IMpassion050) is a global Phase III, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PacHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3, M0).

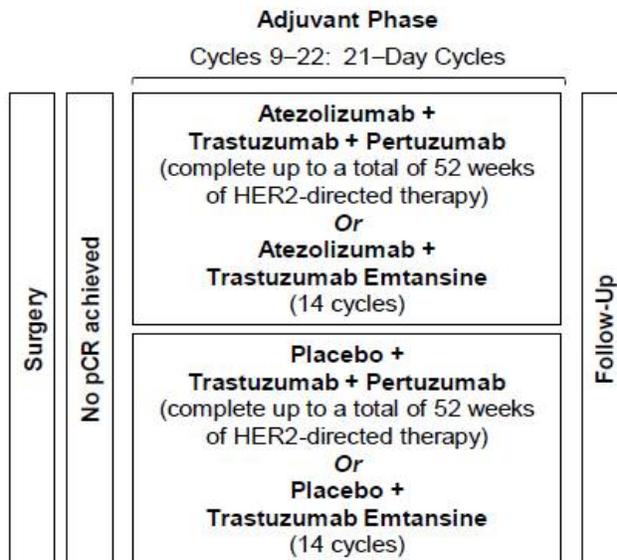
Patients who have histologically confirmed invasive HER2-positive breast cancer with a primary tumor size > 2 cm by radiologic measurement and who are node positive (node-positivity pathologically confirmed by fine-needle aspiration or core-needle biopsy) are eligible. Axillary surgery (including incisional and/or excisional biopsy) prior to neoadjuvant treatment is prohibited. HER2 positivity will be confirmed by a central laboratory. Patients whose tumor tissue is not evaluable for PD-L1 testing by the central laboratory will not be eligible.

[Figure 1](#) presents an overview of the study design.

Figure 1 Study Schema



Treatment options for patients without pCR



Approximately 453 patients will be randomized in a 1:1 ratio to receive either atezolizumab or placebo administered IV in combination with the current standard-of-care therapy for early HER2-positive breast cancer. Treatment assignment will not be unblinded following pCR evaluation. Patients will remain assigned to their initial randomized treatment (atezolizumab or placebo) during the adjuvant phase, irrespective of their pCR result.

Randomization will be stratified by the following factors:

- Stage at diagnosis (T2, T3–4) as determined by the American Joint Committee on Cancer (AJCC) staging system, 8th edition (specifically according to the Anatomic Stage Group rules)
- Hormone receptor status (ER positive and/or PgR positive; ER negative and PgR negative)
 - Patients with hormone receptor–positive disease will be capped at 50%.
- PD-L1 status (IC 0; IC 1/2/3)

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the EBC setting in the PD-L1-positive (IC 1/2/3) and the ITT population on the basis of pathologic complete response (pCR), defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (NAST) (i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition).

2.1 PROTOCOL SYNOPSIS

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

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The co-primary efficacy endpoint of the study is pathological complete response rate (pCR) in the PD-L1-positive (IC 1/2/3) and the ITT populations, defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (NAST) (i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition).

2.2.2 Secondary Efficacy Endpoints

- pCR (ypT0/is ypN0) in the PD-L1-negative (IC 0) population
- pCR (ypT0/is ypN0) based upon hormone receptor status (estrogen receptor [ER]/progesterone receptor [PgR] positive or ER/PgR negative)

- Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause, whichever occurs first, in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- DFS, defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first, in all patients who undergo surgery and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- OS, defined as the time from randomization to death from any cause in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- Mean and mean changes from baseline score in function (role, physical) and global health status (GHS)/HRQoL, as measured by scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) by assessment timepoint, and between treatment arms

2.2.3 Exploratory Efficacy Endpoints

- Mean and mean changes from baseline score in disease/treatment-related symptoms and emotional function, social function by assessment timepoint and between treatment arms as assessed by all symptom items/scales and the emotional, social function scales of the EORTC QLQ-C30
 - Treatment burden as measured by a single item (GP5: “I am bothered by side effects of treatment”) from the physical well-being subscale of the Functional Assessment of Cancer Therapy–General (FACT-G) quality-of-life instrument by assessment of the proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G
 - Utility scores of the EuroQol 5 Dimension, 5-Level (EQ-5D-5L) questionnaire
- German(BA) Disease-free survival (G(BA)DFS) is the time from surgery to the first occurrence of disease recurrence or death from any cause.
- Events defining G(BA)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)
 - Distant recurrence (i.e., evidence of breast cancer in any anatomic site – other than the two above mentioned sites—that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
 - Contralateral invasive breast cancer
 - Ipsilateral or contralateral ductal carcinoma in situ (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 if at all possible).

2.2.4 Pharmacokinetic Endpoints

- Peak and trough (maximum serum concentration observed [C_{max}] and minimum serum concentration under steady-state conditions within a dosing interval [C_{min}]) concentrations of atezolizumab in serum at specified timepoints
- Trough concentration for pertuzumab and trastuzumab in serum at specified timepoints
- Peak and trough concentration for trastuzumab emtansine in serum at specified timepoints

2.2.5 Safety Endpoints

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.2.6 Immunogenicity Endpoints

- Incidence of treatment-emergent anti-drug antibodies (ADAs) to atezolizumab
- Incidence of treatment-emergent ADAs to trastuzumab, pertuzumab, and trastuzumab emtansine

The exploratory immunogenicity endpoint is as follows:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.2.7 Biomarker Endpoints

The secondary biomarker endpoints are as follows:

- pCR (ypT0/is ypN0), EFS, DFS, and OS based upon PIK3CA mutation status

Exploratory biomarker endpoints may include the following:

- pCR (ypT0/is ypN0) based upon stromal TIL infiltration level
- pCR (ypT0/is ypN0) based upon immune gene expression level
- Relationship between biomarkers (and/or changes in biomarkers) in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Association of biomarkers with EFS, DFS and OS
- Association between post-surgical circulating-tumor DNA (ctDNA) and outcome
- On-treatment changes of ctDNA associated with atezolizumab + ddAC-PacHP compared with placebo+ddAC-PacHP and its association with EFS, DFS, and OS

2.3 DETERMINATION OF SAMPLE SIZE

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

- Co-primary efficacy endpoint pCR in the PD-L1-positive population with an allocated α of 0.048
- Co-primary efficacy endpoint pCR in the ITT population with an allocated α of 0.002

The global study will randomize approximately 453 patients in total. Assuming a prevalence of 40% of PD-L1-positive patients, the PD-L1-positive population is estimated to comprise approximately 181 patients.

This sample size will allow for 80% power to detect an improvement in pCR proportion from 70% in the placebo+ddAC-PacHP group to 90% (+20%) in the atezolizumab+ddAC-PacHP group at the 4.8% level of significance (two-sided) assuming a dropout of 7% of the patients (i.e., patients without pCR assessment will be regarded as not achieving pCR resulting in an improvement in pCR proportion from 65% vs. 83%; +18%) in the PD-L1-positive population.

In the ITT population, this sample size will allow for 82.8% power to detect an improvement in pCR proportion from 60% in the placebo+ddAC-PacHP group to 80% (+20%) in the atezolizumab+ddAC-PacHP group at the 0.2% significance level, assuming a dropout of 10% of the patients (i.e., patients without pCR assessment will be regarded as not achieving pCR resulting in an improvement in pCR proportion from 54% vs. 72%; (+18%).

If the co-primary efficacy endpoint pCR in the PD-L1-positive population is significant, the available α of 0.048 will be allocated additionally to the co-primary efficacy endpoint pCR in the ITT population in a hierarchical manner resulting in an alpha of 0.05.

2.4 ANALYSIS TIMING

The primary analysis will take place once all randomized patients have completed neoadjuvant treatment and undergone surgery. The administrative interim efficacy analysis will occur once 227 (50%) patients have completed neoadjuvant treatment and undergone surgery.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Patients are randomized in a 1:1 ratio using a permuted-block randomization method to one of two treatment arms: atezolizumab + neoadjuvant ddAC-PacHP or placebo + neoadjuvant ddAC-PacHP. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the categories defined for the following stratification factors at baseline:

- Stage at diagnosis (T2, T3–4)
- Hormone receptor status (ER positive and/or PgR positive; ER negative and PgR negative)
- PD-L1 status (IC 0; IC 1/2/3)

Enrollment of patients with hormone receptor positive disease will be capped at 50%.

3.2 INDEPENDENT REVIEW FACILITY

No Independent Review Facility is in place for this study.

3.3 DATA MONITORING

The independent Data Monitoring Committee (iDMC) shares with the Sponsor the responsibility to monitor overall patient safety of the Investigational Medicinal Products (IMPs). The iDMC will evaluate unblinded safety data on a regular basis during the study until the analysis of the primary endpoint of pCR, once all patients have completed neoadjuvant therapy and undergone surgery, after which iDMC review of the study data will be discontinued.

The iDMC will also review the unblinded efficacy data at the administrative interim analysis, as described in Section [4.10.1](#).

The iDMC will work according to the guidelines defined in the iDMC Charter. The iDMC Charter contains details regarding the frequency of meetings, guidelines for decision making and process for requesting further information. The iDMC members will review and sign off the charter before the first safety review.

4. STATISTICAL METHODS

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

If extended enrollment in China is initiated, data from this phase will not be included in the primary analysis of global study. A separate analysis will be performed for the China subpopulation (i.e. patients enrolled from mainland China and Taiwan during both global enrollment phase and the extended China enrollment phase).

4.1 ANALYSIS POPULATIONS

4.1.1 Randomized Population

For all efficacy analyses, patients will be assigned to the treatment group to which they were randomized.

4.1.1.1 Intention-to-Treat (ITT) Population

The ITT population is defined as all randomized patients, regardless of whether the assigned study treatment was received.

4.1.1.2 PD-L1-Positive Population

The PD-L1-positive population is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.

4.1.1.3 DFS-Evaluable Population

The DFS-evaluable population is defined as patients in the ITT population who undergo surgery.

4.1.1.4 PD-L1-Positive–DFS-Evaluable Population

The DFS-evaluable population is defined as patients in the PD-L1-positive population who undergo surgery.

4.1.1.5 PRO-Evaluable Population

The PRO-evaluable population is defined as patients in the ITT population with a baseline and at least 1 post-baseline PRO assessment.

4.1.2 Pharmacokinetic-Evaluable Population

The pharmacokinetic (PK)-evaluable population is defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

4.1.3 Safety Population

The safety-evaluable population is defined as patients who received at least one dose of any study drug. For safety analyses, patients will be assigned to treatment groups as treated (atezolizumab vs. placebo), and all patients who received any dose of atezolizumab will be included in the atezolizumab treatment arm.

4.2 ANALYSIS OF STUDY CONDUCT

For all randomized patients (i.e., ITT population), a participant flowchart for depicting the progress of subjects through the phases of the trial will be provided by treatment arm in the CSR, including a complete description of patient disposition specifying the number of randomized, completed and discontinued patients from trial treatment and study with reasons for premature discontinuation.

Documented major protocol deviations including major deviations with regard to the inclusion and exclusion criteria, conduct of the study, patient management, or patient assessment will be tabulated by treatment arm.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (in particular, stratification variables) will be summarized by treatment arm for the ITT and PD-L1-positive populations. Only descriptive analyses are planned; no formal statistical tests will be applied. Continuous variables will be reported and summarized by use of standard measures of central tendency and dispersion (mean, standard deviation, median, ranges and inter-quartile ranges), and categorical (i.e., discrete) data will be reported and summarized by frequencies and percentages.

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

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

4.4 EFFICACY ANALYSIS

4.4.1 Co-Primary Efficacy Endpoint

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PachHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3) as measured by pCR in the ITT and in the PD-L1-positive populations. pCR is established following completion of neoadjuvant therapy and surgery.

pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of NAST (i.e., ypT0/is ypN0 in the current AJCC staging system).

Patients with missing pCR assessment will be counted as not achieving a pCR. Treatment comparison of pCR will be made using Cochran-Mantel-Haenszel test stratified by disease stage (T2 vs. T3–4), hormone receptor status (positive vs. negative) and PD-L1 status (IC 0 vs. IC 1/2/3), if applicable. The 2-sided significance level in the PD-L1-positive population is 4.8% and in the ITT population 0.2%. The stratification factors will be based on data collected by the IxRS at the time of randomization. Confidence intervals for the difference in pCR rate between the two arms will be determined using the normal approximation to the binomial distribution.

A summary table that presents the number and proportion of pCR in each treatment arm, together with the 2-sided 95% CI with use of the Clopper-Pearson method ([Clopper and Pearson 1934](#)) will be produced.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 pCR in Subgroups

pCR in subgroups by hormone receptor status and PD-L1-negative status are defined as secondary efficacy endpoints.

pCR is defined in analogous manner to the primary endpoint and will be analyzed with the same methodology in the subgroups. The stratification factors in the subgroup analysis will be as defined below:

- pCR by hormone receptor status: The stratification factors will be disease stage and PD-L1 status. This endpoint will be additionally analyzed in the subgroups defined by PD-L1 status.
- pCR in PD-L1-negative patients: The stratification factors will be disease stage and hormone receptor status.

4.4.2.2 Event-Free Survival

EFS is defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause, whichever occurs first.

Patients without an event at the time of the 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 at the date of randomization.

EFS will be compared between treatment arms with the use of the log-rank test stratified by the randomization stratification factors collected by the IxRS at the time of randomization and by the adjuvant treatment regimen. The HR for EFS will be estimated using a Cox proportional hazards model. The 95% CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate the median EFS (if reached) for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median EFS for each treatment arm ([Brookmeyer and Crowley 1982](#)). The Kaplan-Meier approach will be also used to estimate landmark EFS rates, including 3-year EFS rates at the final analysis 1-year rates at the primary analysis, and corresponding 95% CIs for each treatment arm. Results from an unstratified analysis will also be provided.

The EFS analysis will be performed approximately 36 months after the randomization of the last patient during the global enrollment phase.

4.4.2.3 Disease-Free Survival

DFS is defined as the time from surgery (i.e., the first date of no disease) to the first documented disease recurrence or death from any cause, whichever occurs first.

Patients who do not undergo surgery at the end of neoadjuvant treatment will be excluded from the analysis of DFS.

Patients without a DFS event at the time of analysis will be censored at the date when they were last known to be alive and event free. Patients who do not have information after surgery will be censored at the date of surgery.

DFS will be analyzed with the use of the same methodology as specified for EFS. The DFS analysis will be performed approximately 36 months after the randomization of the last patient during the global enrollment phase.

The exploratory endpoint German(BA) Disease-Free Survival defined in Section [2.2.3](#) will be analysed in the same way as DFS.

4.4.2.4 Overall Survival

OS is defined as the time from randomization to death from any cause. Patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Patients who do not have information after baseline will be censored at the date of randomization. OS will be analyzed with the use of the same methodology as specified for EFS. The OS analysis will be performed approximately 36 months after the randomization of the last patient during the global enrollment phase.

4.4.2.5 Patient Reported Outcomes of Role and Physical Function and GHS/HRQOL: EORTC Data

The secondary PRO endpoints are mean and mean changes from baseline score in function (role, physical) and GHS/HRQoL. Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for the role function ([Question {Q6, Q7}], physical function [Q1-Q5]), and the GHS/HRQoL (Q29, Q30) scales of the EORTC QLQ-C30 at each assessment timepoint for each arm. The mean (and 95% CI) and median of the absolute scores and the changes from baseline will be reported on patients with a baseline and at least one post-baseline assessment. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and GHS/HRQoL scales ([Osoba et al. 1998](#); [Cocks et al. 2011](#)).

The EORTC 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, if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manual and validation papers of the measure. For subscales with less than 50% of the items completed, the subscale will be considered missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

4.4.3 Exploratory Efficacy Endpoints

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

Summary statistics (mean, 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 and social function scales of the EORTC QLQ-C30 at each assessment timepoint for each arm.

Rules for handling missing data will be the same as those defined in Section 4.4.2.5 for the secondary PRO endpoints measured by the EORTC QLQ-C30.

4.4.3.2 Patient-Reported Outcome of Treatment Burden: FACT-G, GP5 Single-Item Data

A descriptive analysis of absolute scores, change from baseline scores, and the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported for item GP5 (“I am bothered by side effects of treatment”) from the FACT-G physical well-being subscale. Item GP5 from Version 4 of the FACT-G Questionnaire will be scored according to the Functional Assessment of Chronic Illness Therapy scoring manual (Cella 1997).

4.4.3.3 Health Economic EQ-5D-5L Data

Health utility data from the EQ-5D-5L will be evaluated in pharmacoeconomic models. The results from the health economic data analyses will be reported separately from the clinical study report.

4.4.4 Sensitivity Analyses

4.4.5 Subgroup Analyses

To assess the consistency of the study results in patient subgroups defined by key demographic and baseline characteristics, including the stratification factors, subgroup analyses of pCR, EFS, DFS and OS will be performed. Subgroups will include but are not limited to the following characteristics:

- PD-L1 status (IC 0; IC 1/2/3)
- Primary Tumor Stage at diagnosis (T2; T3-4)
- Lymph Node Stage at diagnosis (N1; 2; 3)
- AJCC Stage at diagnosis (II, III)
- Hormone receptor status (ER positive and/or PgR positive; ER negative and PgR negative)
- Age-group (<65; ≥65)
- Race (White; Black; Asian; Other)
- ECOG Performance Status (0; 1)
- Outcome of surgery (pCR, non-pCR) (subgroup analyses of EFS, DFS and OS only)

The analysis of pCR in the PD-L1+ subgroup is a co-primary endpoint and as such is subject to type I error control, as described in Section 4.4.1. All other subgroup analyses will be considered exploratory in nature.

Summary statistics for pCR will include the n (%) of patients achieving pCR by treatment arm within each subgroup level.

Summaries for EFS, DFS and OS, including the unstratified hazard ratio estimated from the Cox-proportional hazards model and Kaplan-Meier estimates of the median (if reached) will be produced separately for each subgroup level.

4.5 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (Cmin and Cmax) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (%CV), and others as appropriate.

The pertuzumab, trastuzumab, and trastuzumab emtansine concentrations in serum will also be tabulated and summarized. Additional PK and PD analyses may be conducted as appropriate.

4.6 SAFETY ANALYSES

Safety will be assessed through summaries of study treatment exposures, adverse events, changes in targeted laboratory and diagnostic test results, changes in vital signs, and immunogenicity as measured by ADAs and will be presented by treatment arm. Full safety analyses will be provided for the neoadjuvant therapy portion of the trial. Selected safety data will also be presented separately according to adjuvant treatment regimen.

4.6.1 Exposure to Study Treatment

Study drug exposure, including but not limited to treatment duration, number of cycles, and dose intensity, will be summarized with descriptive statistics for each study treatment on each treatment arm if deemed appropriate.

4.6.2 Adverse Events

Verbatim descriptions of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v5.0.

Treatment-emergent adverse events, defined as events occurring on or after the first dose of study treatment, will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v5.0 grade, regardless of relationship to study drug as assessed by the investigator. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately:

- Adverse Events

- Adverse events leading to withdrawal of study drug
- Adverse events leading to dose reduction or interruption
- Grade 3/4 adverse events
- Grade 5 adverse events
- Serious adverse events
- Adverse events of special interest
- Selected adverse events on the basis of the safety profile of the study drug

All deaths and causes of death will be summarized.

4.6.3 Laboratory Data

Laboratory data with values outside of the normal ranges will be identified. Relevant laboratory values will be summarized by treatment arm over time, with NCI CTCAE v5.0 Grade 3 and Grade 4 values identified, where appropriate. Clinically relevant shifts from baseline in NCI CTCAE v5.0 grade (defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post baseline) will be also provided by treatment arm. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables.

A Hy's Law analysis will be provided: the finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law).

4.6.4 Vital Signs

Change from baseline in selected vital signs will be summarized by treatment arm.

4.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include all safety evaluable patients, with patients grouped according to treatment received.

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 by treatment group. 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 units 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 are 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 units 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

Biomarker analyses will be performed as follows:

Analysis of pCR by biomarker levels will be stratified by disease stage (T2 vs T3-4), central hormone receptor status, and PD-L1 status.

Central HER2 status by IHC are

- 0/1+
- 2+
- 3+

Central HER2 status by ISH are

- pos
- neg

PD-L1 expression level on tumor-infiltrating immune cells

- IC 0
- IC 1
- IC 2
- IC 3

PIK3CA mutation status

- mutated
- wildtype

of pCR, EFS, DFS, and OS may be analyzed according to the status of other biomarkers , e.g. for PIK3CA mutation status, as appropriate.

Main results are presented in the CSR, the remaining results will be presented in a separate report.

4.9 MISSING DATA

In efficacy analyses of pCR, patients with a missing pCR assessment will be counted as not achieving pCR in the analysis.

The analyses of EFS and OS will include all randomized patients, and the analysis of DFS will include all patients who undergo surgery. No patients will be excluded from analysis due to missing data. Censoring strategies for patients without an event are described in section [4.4.2](#).

The rules for missing data associated with the patient reported outcome questionnaires are detailed in Section [4.4.2.5](#).

4.10 INTERIM ANALYSES

4.10.1 Planned Interim analysis

In order to extract information from data accumulated thus far for reasons external to the study (administrative objective, to inform the initiation of a possible subsequent trial), an administrative interim efficacy analysis of pCR is planned to take place once 227 patients have been enrolled, completed neoadjuvant treatment and undergone surgery. The administrative interim analysis is performed without any intention to stop the trial. However, a minimum alpha of 0.0001 will be spent to protect the overall type I error. The interim analysis will be performed by the iDCC, an external statistical group, to ensure the Sponsor study team personnel remain blinded. The results will be reviewed by the iDMC. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter.

The iDMC should give a positive recommendation for the possible subsequent trial if the protocol assumptions are met in either the PD-L1-positive or ITT population. The difference in pCR rates should be at least 18% in either the PD-L1-positive or the ITT population.

4.10.2 Optional Interim Analysis

The Sponsor may choose to conduct interim efficacy analyses after the primary analysis for pCR and before the final analysis for EFS and OS, if needed (e.g., for regulatory or publication purposes). The decision to conduct an optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in an amendment to the Sponsor's Statistical Analysis Plan prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel who will have full access to unblinded data. Access to treatment assignment information will follow the Sponsor's standard procedures.

4.11 CHINA SUBPOPULATION ANALYSES

After completion of the global enrollment phase, additional patients may continue to be enrolled in China in an extended China enrollment phase to achieve a total of approximately 70 patients from mainland China and Taiwan. The China subpopulation will include all patients of Chinese ancestry enrolled from mainland China and Taiwan during both the global enrollment phase and the extended China enrollment phase.

The China subgroup analysis will be performed based on the China subpopulation. The sample size of the China subpopulation will provide >70% probability of showing consistent treatment benefit assessed by pCR rate compared with that estimated from the global populations. The China subpopulation is not powered to demonstrate

statistical significance in terms of efficacy; thus, no formal hypothesis testing will be performed.

The analyses for the China subpopulation will be performed in a similar way as done for the global population, or summarized descriptively as appropriate. Results from these analyses will be summarized separately.

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Appendix 1

Protocol Synopsis

TITLE: A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH NEOADJUVANT DOXORUBICIN + CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL + TRASTUZUMAB + PERTUZUMAB IN EARLY HER2-POSITIVE BREAST CANCER

PROTOCOL NUMBER: BO40747

VERSION NUMBER: 4

EUDRACT NUMBER: 2018-001881-40

NCT NUMBER: NCT03726879

IND NUMBER: 123277

TEST PRODUCT: Atezolizumab (RO5541267),
Pertuzumab (RO4368451),
Trastuzumab (RO0452317),
Trastuzumab emtansine (RO5304020)

PHASE: Phase III

INDICATION: Early HER2-positive breast cancer

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study (also known as IMpassion050) will evaluate the efficacy and safety of atezolizumab compared with placebo when given in combination with neoadjuvant dose-dense anthracycline (doxorubicin)+cyclophosphamide followed by paclitaxel+trastuzumab+pertuzumab (ddAC-PacHP) in patients with early human epidermal growth factor 2 (HER2)-positive breast cancer at high risk of recurrence (T2-4, N1-3, M0). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Co-Primary Efficacy Objective

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab+ddAC-PacHP compared with placebo+ddAC-PacHP in the early breast cancer (EBC) setting in the PD-L1-positive (IC 1/2/3) and the intent-to-treat (ITT) populations on the basis of the following endpoint:

- Pathological complete response (pCR), defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/is ypN0 in the current American Joint Committee on Cancer [AJCC] staging system, 8th edition) in the PD-L1-positive and ITT populations

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab+ddAC-PacHP compared with placebo+ddAC-PacHP in the EBC setting on the basis of the following endpoints:
 - pCR (ypT0/is ypN0) based upon hormone receptor status (estrogen receptor [ER]/progesterone receptor [PgR] positive or ER/PgR negative)
 - pCR (ypT0/is ypN0) in the PD-L1-negative (IC 0) population
 - Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause, whichever occurs first, in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
 - Disease-free survival (DFS), defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first, in all patients who undergo surgery and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
 - Overall survival (OS), defined as the time from randomization to death from any cause in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- To evaluate patient-reported outcomes (PROs) of function (role, physical) and health-related quality of life (HRQoL) associated with atezolizumab+ddAC-PacHP compared with placebo+ddAC-PacHP, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), on the basis of the following endpoint:
 - Mean and mean changes from baseline score in function (role, physical) and global health status (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

The exploratory efficacy objectives for this study are as follows:

- To evaluate PROs of disease/treatment-related symptoms and emotional, social function associated with atezolizumab+ddAC-PacHP by the EORTC QLQ-C30 on the basis of the following endpoint:
 - Mean and mean changes from baseline score in disease/treatment-related symptoms and emotional, social function by assessment timepoint and between treatment arms as assessed by all symptom items/scales and the emotional, social function scales of the EORTC QLQ-C30
- To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to ddAC-PacHP compared with placebo+ddAC-PacHP, as measured by a single item (GP5: “I am bothered by side effects of treatment”) from the physical well-being subscale of the Functional Assessment of Cancer Therapy–General (FACT-G) quality-of-life instrument on the basis of the following endpoint:
 - 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 EuroQol 5 Dimension, 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement on the basis of the following endpoint:
 - Utility scores of the EQ-5D-5L questionnaire

Safety Objective

The safety objective for this study is to evaluate the safety of atezolizumab+ ddAC-PacHP compared with placebo+ddAC-PacHP in the neoadjuvant setting and the safety of atezolizumab combined with trastuzumab+pertuzumab (or combined with trastuzumab emtansine) compared with placebo combined with trastuzumab+pertuzumab (or combined with trastuzumab emtansine) in the adjuvant EBC setting on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of atezolizumab, pertuzumab, and trastuzumab when given in combination and of atezolizumab and trastuzumab emtansine when given in combination on the basis of the following endpoints:

- Peak and trough (maximum serum concentration observed [C_{max}] and minimum serum concentration under steady-state conditions within a dosing interval [C_{min}]) of atezolizumab concentrations in serum at specified timepoints
- Trough concentration for pertuzumab and trastuzumab in serum at specified timepoints
- Peak and trough concentration for trastuzumab emtansine in serum at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab, trastuzumab, pertuzumab, and trastuzumab emtansine on the basis of the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs) to atezolizumab and its impact on pharmacokinetics, efficacy, and safety
- Incidence of treatment-emergent ADAs to trastuzumab, pertuzumab, and trastuzumab emtansine

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objectives

The secondary biomarker objectives for this study are as follows:

- To evaluate pCR (ypT0/is ypN0), EFS, DFS, and OS based upon PIK3CA mutation status

The exploratory biomarker objectives for this study are as follows:

- To evaluate pCR (ypT0/is ypN0) based upon stromal tumor-infiltrating lymphocyte (TIL) infiltration level
- To evaluate pCR (ypT0/is ypN0) based upon immune gene expression level
- To identify biomarkers and/or changes in biomarkers that are predictive of response to atezolizumab ddAC-PacHP (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab+ddAC-PacHP, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of atezolizumab+ddAC-PacHP activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:
 - Relationship between biomarkers (or changes in biomarkers) in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

- To evaluate biomarkers in association with EFS, DFS, and OS
- To evaluate post-surgical circulating-tumor DNA (ctDNA) with outcome
- To evaluate ctDNA on-treatment changes associated with atezolizumab+ddAC-PacHP compared with placebo+ddAC-PacHP and to evaluate its association with EFS, DFS, and OS

Study Design

Overview of Study Design

This is a global Phase III, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PacHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3, M0).

Patients who have histologically confirmed invasive HER2-positive breast cancer with a primary tumor size > 2 cm by *any* radiologic measurement and who are node positive (node-positivity pathologically confirmed by fine-needle aspiration or core-needle biopsy) are eligible. Axillary surgery (including sentinel-node biopsy) prior to neoadjuvant treatment is prohibited. HER2 positivity of the primary breast tumor will be confirmed by a central laboratory. Patients whose tumors are not centrally confirmed to be HER2-positive will not be eligible. Patients whose tumor tissue is not evaluable for PD-L1 by central laboratory will not be eligible. Patients who do not initially meet eligibility criteria may be rescreened once.

Patients who have consented and are eligible will be randomized in a 1:1 ratio to receive either atezolizumab or placebo administered IV in combination with the current standard neoadjuvant therapy for early HER2-positive breast cancer.

Randomization will be stratified by the following factors:

- Stage at diagnosis (T2, T3–4) as determined by the AJCC staging system, 8th edition (specifically according to the Anatomic Stage Group rules)
- Hormone receptor status (ER positive and/or PgR positive; ER negative and PgR negative)
Hormone receptor–positive status will be capped at 50%
- PD-L1 status (IC 0; IC 1/2/3)

Study treatment administration should begin within 7 days after randomization.

During the neoadjuvant phase (i.e., prior to surgery; Cycles 1–8), all patients will receive:

- Atezolizumab or placebo 840 mg IV every 2 weeks (Q2W) for 4 cycles (Cycles 1–4)
- ddAC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² IV) given with granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor, or pegylated granulocyte colony-stimulating factor support in accordance to local guidelines Q2W for 4 cycles (Cycles 1–4)

Followed by:

- Atezolizumab or placebo 1200 mg IV every 3 weeks (Q3W) for 4 cycles (Cycles 5–8)
- Paclitaxel 80 mg/m² IV every week (QW) for 4 cycles (Cycles 5–8)
- Trastuzumab 6 mg/kg IV (with an initial 8-mg/kg IV loading dose) Q3W for 4 cycles (Cycles 5–8)
- Pertuzumab 420 mg IV (with an initial 840-mg IV loading dose) Q3W for 4 cycles (Cycles 5–8)

A cycle will be considered missed during the neoadjuvant phase if the subsequent cycle cannot be administered within 28 days of the last dose for Cycles 1–4 or within 42 days of the last dose for Cycles 5–8. In this situation, make-up treatment of missed cycles *of chemotherapies* is permitted post-surgery prior to the adjuvant phase (described below).

During the adjuvant phase (i.e., post-surgery; Cycles 9–22), the following study treatments will be continued Q3W to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting:

- Atezolizumab/placebo 1200 mg IV Q3W
- Trastuzumab 6 mg/kg IV (with an initial 8-mg/kg IV loading dose) Q3W
- Pertuzumab 420 mg IV (with an initial 840-mg IV loading dose) Q3W

Patients who do not achieve a pCR as defined in the protocol (i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition) have the option of receiving adjuvant treatment as outline above or alternatively:

- Atezolizumab or placebo as per initial treatment assignment 1200 mg IV Q3W combined with trastuzumab emtansine 3.6 mg/kg IV Q3W

Treatment assignment will not be unblinded following pCR evaluation. The treatment decision for patients who do not achieve a pCR after neoadjuvant therapy is per investigator discretion.

Atezolizumab/placebo+trastuzumab+pertuzumab will be *given to* complete 52 weeks of HER2-directed therapy, regardless of the number of cycles administered. Adjuvant atezolizumab/placebo+trastuzumab emtansine will be given for 14 cycles. If trastuzumab emtansine is discontinued for toxicity not considered related to the trastuzumab component of the drug, treatment can be switched to trastuzumab and pertuzumab with atezolizumab/placebo to complete a total of 1 year of HER2-targeted therapy.

Patients who discontinue neoadjuvant therapy early as a result of disease progression must be discontinued from all study treatment, will be managed as per local practice, and will be followed for survival only. Any patient who receives non-protocol therapy prior to surgery will be discontinued from study treatment and will be managed as per local practice; these patients will remain on study for survival follow-up. For patients who do not achieve pCR, it is recommended to continue on study treatment with the option to receive atezolizumab/placebo + HP or atezolizumab/placebo + trastuzumab emtansine on the basis of a benefit-risk assessment for the individual patient. Alternatively, as per investigator discretion, local clinical guidelines for management of non-pCR patients may be followed; the patient should be followed for survival and subsequent anti-cancer therapy.

Patients who discontinue one or more of the study treatment components due to toxicity should not be automatically withdrawn from all study treatments. Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in the protocol.

Patients who discontinue early from all components of the pre- or post-operative study treatment should still remain in survival follow-up. Patients who discontinue prematurely from the study will not be replaced.

The primary efficacy endpoint (pCR; ypT0/is ypN0) will be established via local review following completion of neoadjuvant therapy and surgery. In line with pCR guidance from U.S. Food and Drug Administration (FDA), pathologists who review study specimens will conduct review of study specimens in a blinded manner. Pathologists must utilize the evaluations and assessments outlined in the study pathology manual. Surgery should be performed at least 14 days after the last dose of neoadjuvant study treatment but no later than 6 weeks after the last infusion. Platelet counts should be checked prior to surgery and should be $\geq 75,000$ cells/ μ L. Patients must undergo full axillary lymph node dissection at the time of definitive surgery. Sentinel lymph node procedure alone is not permitted. If surgically feasible, it is recommended that at least 10 lymph nodes are removed for pathologic examination. For sentinel nodes involving the internal mammary chain, refer to local, national, or international guidelines. Level III axillary dissections should be performed for patients with gross disease in the Level II nodes. The first dose of postoperative treatment should not start until 2 weeks after surgery but should be administered within 45 days of surgery. Postoperative patient management for those in either treatment arm may include radiotherapy and hormonal therapy as clinically indicated and in accordance with standard local clinical practice.

An independent Data Monitoring Committee (iDMC) will evaluate safety data and study conduct on a regular basis during the study until the analysis of the primary endpoint of pCR, after which

iDMC review of the study data will be discontinued. An administrative interim analysis of efficacy will also take place once 227 patients have been enrolled, completed neoadjuvant treatment, and undergone surgery. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles, responsibilities, and timing of iDMC meetings. To assess the potential cardiac toxicity of the combination of anthracyclines and atezolizumab, the iDMC will review data from a cardiac safety cohort involving additional cardiac monitoring in the first 26 patients enrolled (approximately 13 patients in the control arm and approximately 13 patients in the atezolizumab arm) after all 26 patients have completed or have discontinued the neoadjuvant portion of the study.

A real-time safety assessment of the first 12 patients enrolled (approximately 6 patients in the control arm and approximately 6 patients in the atezolizumab arm) will be conducted without stopping accrual. This safety evaluation by the Sponsor of blinded data and the iDMC of unblinded data will be conducted after the first 12 patients have completed 6 cycles of neoadjuvant therapy (4 cycles of atezolizumab/placebo+ddAC and 2 cycles of atezolizumab/placebo+PacHP).

See the protocol for details regarding the iDMC.

Following completion of study treatment and surgery, all patients will continue to be followed for efficacy, safety, and PRO objectives until the end of the study. No interim efficacy analyses for early stopping are planned, although an administrative interim analysis of efficacy is planned. Safety assessments will include the occurrence and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Tumor tissue will also be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator, at the time of disease recurrence. These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab.

Number of Patients

Approximately 453 patients with cT 2–4, cN1–3, cM0 HER2-positive breast cancer (tumor >2 cm and lymph node positive) will be enrolled in this study. After completion of the global enrollment phase, additional patients may be enrolled at sites in China in an extended China enrollment phase to ensure a total of approximately 70 patients in a China subpopulation (patients of Chinese ancestry from mainland China and Taiwan).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age \geq 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Confirmed diagnosis of HER2-positive breast cancer, and hormonal and PD-L1 status, as documented through central testing of a representative tumor tissue specimen, is required.

A formalin-fixed paraffin-embedded tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted prior to study enrollment. Any deviation of the material requirements are only allowed after Sponsor's approval has been obtained.

HER2-positive status will be determined based on pretreatment breast biopsy material and defined as an *immunohistochemistry* (IHC) score of 3+ or positive by in situ hybridization (ISH) prospectively assessed by a central laboratory prior to study enrollment. ISH positivity is defined as a ratio of ≥ 2 for the number of HER2 gene copies to the number of signals for chromosome 17 copies. A central laboratory will perform both IHC and ISH assays; however, only one positive result is required for eligibility.

PD-L1 status through measurement of IHC will be used for stratification. *The maximum PD-L1 score assessed among samples submitted for eligibility will be used as the PD-L1 score for the patient.*

ER/PgR status will be determined centrally based on pretreatment breast biopsy material according to the American Society of Clinical Oncology (ASCO) and the College of American Pathologists guidelines.

- Primary breast tumor size of > 2 cm by any radiographic measurement (see the protocol for additional details)
- Stage at presentation: T2–T4, N1–N3, M0 as determined by AJCC staging system, 8th edition (specifically in accordance with Anatomic Stage group rules)
- Pathologic confirmation of nodal involvement with malignancy must be determined by fine-needle aspiration or core-needle biopsy. Surgical excision of lymph nodes (e.g., sentinel lymph node biopsy and axillary lymph node biopsy) is not permitted.
- Patients with multifocal tumors (more than one mass confined to the same quadrant as the primary tumor) are eligible provided at least one focus is sampled and centrally confirmed as HER2-positive.
- Patients with multicentric tumors (multiple tumors involving more than one quadrant) are eligible provided all discrete lesions are sampled and centrally confirmed as HER2-positive.

In patients with multifocal or multicentric breast cancer, the largest lesion should be measured to determine T stage.

- Patient agreement to undergo appropriate surgical management, including axillary lymph node surgery and partial or total mastectomy, after completion of neoadjuvant treatment
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Baseline *left ventricular ejection fraction* (LVEF) $\geq 55\%$ measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
 - ANC $\geq 1.5 \times 10^9/L$ (1500 cells/ μ L) without granulocyte colony-stimulating factor (G-CSF) support
 - Lymphocyte count $\geq 0.5 \times 10^9/L$ (500 cells/ μ L)
 - Platelet count $\geq 100 \times 10^9/L$ (100,000 cells/ μ L) without transfusion
 - Hemoglobin ≥ 90 g/L (9 g/dL)
 - Patients may be transfused to meet this criterion
 - AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN)
 - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:
 - Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
 - Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
 - Serum albumin ≥ 25 g/L (2.5 g/dL)
 - For patients not receiving therapeutic anticoagulation: *international normalized ratio* (INR) or *activated partial thromboplastin time* (aPTT) $\leq 1.5 \times$ ULN within 14 days prior to initiation of study treatment
 - For patients receiving therapeutic anticoagulation:
 - INR or aPTT within therapeutic limits for at least 1 week immediately prior to initiation of study treatment
 - Stable anticoagulant regimen and stable INR during the 14 days immediately preceding initiation of study treatment
- 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.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, 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 5 months after the final dose of atezolizumab/placebo, 6 months after the final dose of doxorubicin, 12 months after the final dose of cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last. Women must refrain from donating eggs during this 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, copper intrauterine devices, hormonal contraceptives that inhibit ovulation, and hormone-releasing intrauterine devices in women with hormone receptor-negative tumors only; the use of hormonal contraceptives and hormone releasing intrauterine devices are prohibited in women with hormone receptor-positive tumors.

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 acceptable methods of contraception.

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

With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 final dose of doxorubicin and/or cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last. Men must refrain from donating sperm during this same period. Male patients are encouraged to seek advice regarding cryoconservation of sperm prior to commencing study treatment because of the possibility of infertility with chemotherapy.

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of doxorubicin and/or cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last 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 acceptable methods of contraception.

- For patients enrolled in the extended China enrollment phase: current resident of mainland China and of Chinese ancestry

The China subpopulation will consist of patients enrolled at sites in mainland China and Taiwan who are of Chinese ancestry.

Exclusion Criteria

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

- Prior history of invasive breast cancer
- Stage IV (metastatic) breast cancer
 - Baseline tumor staging determination should be performed in alignment with AJCC staging system, 8th edition (specifically in accordance with Anatomic Stage group rules).
- Patients with synchronous bilateral invasive breast cancer
- *Patients with hormone receptor-positive disease (estrogen receptor-positive and/or progesterone receptor-positive) will be excluded once approximately 227 patients (50% of the total target sample size) with hormone receptor-positive disease have been enrolled*
- Prior systemic therapy for treatment of breast cancer
- Previous therapy with anthracyclines or taxanes for any malignancy
- Ulcerating or inflammatory breast cancer (e.g., erythema and/or dermal involvement, and/or pathologic detection of tumor cells in dermal lymphatics)
- Undergone incisional and/or excisional biopsy of primary tumor and/or axillary lymph nodes
- Sentinel lymph node procedure or axillary lymph node dissection prior to initiation of neoadjuvant therapy
- History of other malignancy within 5 years prior to screening, with the exception of those patients who have a negligible risk of metastasis or death (e.g., 5-year OS of > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Cardiopulmonary dysfunction as defined by any of the following prior to randomization:
 - History of congestive heart failure of any classification
 - 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 > 180 mmHg and/or diastolic blood pressure > 100 mmHg)
 - Evidence of transmural infarction on ECG
 - Requirement for oxygen therapy
- Dyspnea at rest
- 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 antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see the protocol for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
 - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid-replacement hormone are eligible for the study.
 - Patients with controlled type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the 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 of following conditions are met:

- Rash must cover < 10% of body surface area (BSA).
 - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
 - 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, or 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.
 - Active tuberculosis
 - 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 the study
 - Severe infection 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 antibiotics within 2 weeks (IV antibiotics) or 5 days (oral antibiotics) prior to initiation of study treatment
 - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study.
 - Prior allogeneic stem cell or solid organ transplantation
 - Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug and may affect the interpretation of the results, or may render the patient at high risk from treatment complications
 - Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab/placebo treatment or within 5 months after the final dose of atezolizumab/placebo
 - Treatment with investigational therapy within 28 days prior to initiation of study treatment
 - Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T lymphocyte-associated protein-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
 - Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
 - Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor- α [TNF- α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

Cyclophosphamide as part of the study treatment

Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.

Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to the components of the paclitaxel, cyclophosphamide, or doxorubicin formulations
- Known allergy or hypersensitivity to trastuzumab or pertuzumab formulations
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab/placebo, 6 months after the final dose of doxorubicin, 12 months after the final dose of cyclophosphamide, 6 months after the final dose of paclitaxel, or 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last

Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

Exclusions Related to Trastuzumab Emtansine in the Adjuvant Setting:

- Patients who achieved pCR defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition)
- Evidence of clinically evident gross residual or recurrent disease following neoadjuvant therapy and surgery
- Unable to complete surgery with curative intent after conclusion of neoadjuvant systemic therapy
- Patient discontinued treatment with trastuzumab because of toxicity during the neoadjuvant phase of the study
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Patients with *current* Grade ≥ 2 peripheral neuropathy
- Prior treatment with trastuzumab emtansine
- Serum AST, ALT, and alkaline phosphatase not within $\leq 1.5 \times \text{ULN}$
- Serum total bilirubin not within normal range ($\leq 1.0 \times \text{ULN}$)
 - Except for patients with Gilbert's syndrome, for whom direct bilirubin should be within the normal range
- Serum creatinine not within $< 1.5 \times \text{ULN}$

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 36 months after the last patient is enrolled in the global study (i.e., excluding the extended China enrollment phase).

For patients randomized during the extended China enrollment phase, the end of the study is set as the same date as the end of the global study (i.e., expected to occur approximately 36 months after the last patient is enrolled in the global study).

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 54 months, assuming a recruitment period of approximately 18 months, and follow-up for 36 months from the date of enrollment of the last patient in the global study. The Sponsor may decide to terminate the study at any time.

Investigational Medicinal Products

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

Atezolizumab and Placebo

During the neoadjuvant phase, atezolizumab/placebo will be administered by IV infusion at a fixed dose of 840 mg on Day 1 of each 14-day cycle during Cycles 1–4, and 1200 mg on Day 1 of each 21-day cycle during Cycles 5–8. During the adjuvant phase (post-operatively), atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (maximum of 22 cycles [neoadjuvant+adjuvant phases]). Atezolizumab/placebo should be administered as the first infusion.

Treatment will continue as scheduled or until *disease* progression, recurrence of disease, or unmanageable toxicity.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see the protocol. Atezolizumab infusions will be administered per the instructions outlined in the protocol.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the protocol.

No dose modification for atezolizumab is allowed.

Pertuzumab

Pertuzumab is given as a fixed non-weight-based dose of 840-mg IV loading dose, then 420 mg IV Q3W. Pertuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting.

Atezolizumab/placebo should be administered prior to pertuzumab and trastuzumab. The order of administration of pertuzumab and trastuzumab is according to investigator preference.

The initial dose of pertuzumab will be administered over 60 (\pm 10) minutes, and patients will be observed for a further 60 minutes. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 (\pm 10) minutes, and patients will be observed for a further 30 minutes for infusion-related symptoms such as fever or chills. All infusion-related symptoms must have resolved before trastuzumab or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in the protocol. No dose reductions are allowed for pertuzumab. If the patient misses a dose of pertuzumab for any cycle and the time between doses is \geq 6 weeks, a reloading dose of pertuzumab (840 mg) should be given. Subsequent maintenance pertuzumab (420 mg) will then be given Q3W, starting 3 weeks later.

If the interval between the first dose of adjuvant pertuzumab and the last dose of neoadjuvant pertuzumab exceeds 6 weeks, a reloading dose of 840 mg of pertuzumab is required.

Trastuzumab

Trastuzumab is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. Trastuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. Atezolizumab/placebo should be administered prior to pertuzumab and trastuzumab. The order of administration of pertuzumab and trastuzumab is according to investigator preference.

Weight should be recorded during screening and on Day 1 of each cycle for all patients. The baseline weight for a patient will be that measured on Cycle 1, Day 1. The amount of trastuzumab to be administered must be recalculated if the patient's body weight has changed by $>$ 10% (increased or decreased) from the Cycle 1, Day 1 weight. The amount of trastuzumab administered is calculated according to the patient's actual body weight, with no upper limit.

The initial dose of trastuzumab will be administered over 90 (\pm 10) minutes, and patients will be observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever or chills. Interruption or slowing of the infusion may help control such symptoms and

may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (\pm 10) minutes, and patients will be observed for a further 30 minutes. All infusion-related symptoms must have resolved before pertuzumab or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions. Guidelines for dosage modification and treatment interruption or discontinuation are provided in the protocol. No dose reductions are allowed for trastuzumab. If the patient misses a dose of trastuzumab for any cycle and the time between doses is \geq 6 weeks, a reloading dose of trastuzumab (8 mg/kg) should be given. Subsequent maintenance trastuzumab (6 mg/kg) doses will then be given Q3W, starting 3 weeks later.

If the interval between the first dose of adjuvant trastuzumab and the last dose of neoadjuvant trastuzumab exceeds 6 weeks, a reloading dose of 8 mg/kg of trastuzumab is required.

Trastuzumab Emtansine

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W. The dose of trastuzumab emtansine administered will be determined on the basis of the baseline weight of the patient. Weight will be measured at each visit and the dose must be re-adjusted for weight changes \geq 10% compared with the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, in accordance to local practice. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed, following the dose reduction levels provided in the protocol. Once a dose has been reduced for an adverse event(s), it must not be re-escalated.

If the timing of a protocol-mandated procedure, such as administration of trastuzumab emtansine, coincides with a holiday that precludes the procedure, the procedure should be performed within 3 business days of the scheduled date and, when possible, at the earliest following date with subsequent protocol-specified procedures rescheduled accordingly.

Trastuzumab emtansine should be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Trastuzumab emtansine will be administered after the infusion of atezolizumab or placebo.

Chemotherapy

Chemotherapy will be administered in the neoadjuvant setting as follows:

- Doxorubicin 60 mg/m² IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4); with
- Cyclophosphamide 600 mg/m² IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4); followed by
- Paclitaxel 80 mg/m² IV weekly for 12 continuous weeks (Cycles 5–8)

The dose of chemotherapy is calculated according to the patient's BSA. The BSA and the amount of drug administered must be recalculated if the patient's body weight has changed by $>$ 10% (increased or decreased) from baseline. Recalculation of the amount of drug administered on the basis of smaller changes in body weight or BSA is at the investigators' discretion.

There is no mandatory delay between atezolizumab/placebo and ddAC chemotherapy, assuming the infusion is well tolerated.

See the protocol for details on the dosage and administration of doxorubicin, cyclophosphamide, and paclitaxel.

Statistical Methods

Primary Analysis

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PacHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3) as measured by pCR in the ITT and in the PD-L1-positive populations. pCR is established following completion of neoadjuvant therapy and surgery.

pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of NAST (i.e., ypT0/is ypN0 in the current AJCC staging system).

Patients with missing pCR assessment will be counted as not achieving a pCR. Treatment comparison of pCR will be made using Cochran-Mantel-Haenszel test stratified by disease stage (T2 vs. T3–4), hormone receptor status (positive vs. negative) and PD-L1 status (IC 0 vs. IC 1/2/3), if applicable. The 2-sided significance level in the PD-L1-positive population is 4.8% and in the ITT population 0.2%. The stratification factors will be based on data collected by the *interactive voice/web response system* (IxRS) at the time of randomization. Confidence intervals for the difference in pCR rate between the two arms will be determined using the normal approximation to the binomial distribution.

A summary table that presents the number and proportion of pCR in each treatment arm, together with the 2-sided 95% CI with use of the Clopper-Pearson method ([Clopper and Pearson 1934](#)) will be produced.

Determination of Sample Size

The global study will randomize approximately 453 patients in total. Assuming a prevalence of 40% of PD-L1-positive patients (defined as tumors with a PD-L1 expression level of IC 1/2/3), the PD-L1-positive population is estimated to comprise approximately 181 patients.

Type I Error Control

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

- Co-primary efficacy endpoint of pCR, as defined in the protocol, in the PD-L1-positive population with an allocated α of 0.048
- Co-primary efficacy endpoint of pCR, as defined in the protocol, in the ITT population with an allocated α of 0.002

In the PD-L1-positive population, this sample size will allow for 80% power to detect an improvement in pCR proportion from 70% in the placebo+ddAC-PacHP to 90% (+20%) in the atezolizumab+ddAC-PacHP group at the 4.8% level of significance (two-sided) assuming a dropout of 7% of the patients (i.e., patients without pCR assessment will be regarded as not achieving pCR resulting in an improvement in pCR proportion from 65% to 83%; +18%).

In the ITT population, this sample size will allow for 82.8% power to detect an improvement in pCR proportion from 60% in the placebo + ddAC-PacHP to 80% (+20%) in the atezolizumab+ddAC-PacHP group at the 0.2% level of significance (two-sided), assuming a dropout of 10% of the patients (i.e., patients without pCR assessment will be regarded as not achieving pCR resulting in an improvement in pCR proportion from 54% to 72%; +18%).

Interim Analyses

In order to extract information from data accumulated thus far for reasons external to the study (administrative objective *to inform the initiation of a possible subsequent trial*), an administrative interim efficacy analysis of pCR is planned to take place once 227 patients have been enrolled, completed neoadjuvant treatment and undergone surgery. The administrative interim analysis is performed without any intention to stop the trial. However, a minimum alpha of 0.0001 will be spent to protect the overall type I error. The interim analysis will be performed by the *independent Data Coordinating Center* (iDCC), an external statistical group, to ensure the Sponsor study team personnel remain blinded. The results will be reviewed by iDMC. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter.

The rationale and methods, including those to be used for the assessment and protection of the overall type I error, will be documented in the SAP. Details will also be included in the iDMC Charter.

China Subpopulation Analyses

After completion of the global enrollment phase, additional patients may continue to be enrolled in China in an extended China enrollment phase to achieve a total of approximately 70 patients from mainland China and Taiwan. The China subpopulation will include all patients of Chinese

ancestry enrolled from mainland China and Taiwan during both the global enrollment phase and the extended China enrollment phase.

The China subgroup analysis will be performed based on the China subpopulation. The sample size of the China subpopulation will provide >70% probability of showing consistent treatment benefit assessed by pCR rate compared with that estimated from the global populations. The China subpopulation is not powered to demonstrate statistical significance in terms of efficacy, thus no formal hypothesis testing will be performed.

The analyses for the China subpopulation will be performed in a similar way as done for the global population, or summarized descriptively as appropriate. Results from these analyses will be summarized separately. Further details can be found in the *Statistical Analysis Plan*.

Appendix 2 Schedule of Assessments

	Screening/ Baseline ^a		Treatment Cycles										Pre- Surgery Visit/ Surgery ^b	Adjuvant Phase ^c (Cycles 9–22) 21-Day Cycles	Treatment Discontinuation/Early Termination Visit ^d	Follow- Up ^e
			Neoadjuvant Phase Cycles 1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles								Day 1 of Each Cycle (± 3 days)	Day 1 of Each Cycle (± 3 days)				
	Days –28 to –1	Days –14 to –1	Day 1 of Each Cycle (± 3 days)										≤ 30 Days after Final Dose			
			1	2	3	4	5	6	7	8						
Informed consent ^f	x															
Baseline tumor tissue sample ^g	x															
Demographic data	x															
Medical history and baseline conditions	x															
Disease status assessment ^h	x		x	x	x	x	x	x	x	x	x		x	x	x	
Tumor staging ⁱ	x															
Bilateral mammogram ^j	x												x	x		
Surgical treatment plan ^k	x											x				
Pathologic response assessment ^l												x				
Vital signs ^m	x		x	x	x	x	x	x	x	x	x		x	x		
Weight	x		x	x	x	x	x	x	x	x	x		x			
Height	x															
Complete physical examination ⁿ	x										x			x		
Limited physical examination ^o			x	x	x	x	x	x	x	x			x			

	Screening/ Baseline ^a		Treatment Cycles										Adjuvant Phase ^c (Cycles 9–22) 21-Day Cycles	Treatment Discontinuation/Early Termination Visit ^d	Follow- Up ^e
			Neoadjuvant Phase Cycles 1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles					Pre- Surgery Visit/ Surgery ^b	Day 1 of Each Cycle (± 3 days)						
	Days –28 to –1	Days –14 to –1	Day 1 of Each Cycle (± 3 days)								Day 1 of Each Cycle (± 3 days)	≤ 30 Days after Final Dose			
			1	2	3	4	5		6	7			8		
ECOG Performance Status ^p	x		x				x			x			x	x	
ECHO/MUGA scan ^q	x		Refer to footnote "q"										x	x	
ECG (12-lead) ^r	x		As clinically indicated												
Hematology ^s		x ^t	x	x	x	x	x	x	x	x			x	x	
Chemistry ^u		x ^t	x	x	x	x	x	x	x	x			x	x	
Pregnancy test ^v		x	x	x	x	x	x	x	x	x			x	x	x
Coagulation (INR, aPTT)		x ^t								x				x	
TSH, free T3 (or total T3), free T4 ^w	x ^t		x					x					x	x	
HIV, HBV, and HCV serologies	x														
Urinalysis ^x	x		As clinically indicated												
EORTC QLQ-C30, EQ-5D-5L ^y			x	x	x	x	x	x	x	x			x	x	x
FACT-G, single-item GP5 ^{y, z}				x	x	x	x	x	x	x			x	x	x
Serum autoantibody sample ^{aa}	x														
PK samples and ADA samples	See Appendix 2 for detailed schedule.														
Blood and plasma sample for biomarkers	See Appendix 3 for detailed schedule.														

	Screening/ Baseline ^a		Treatment Cycles										Adjuvant Phase ^c (Cycles 9–22) 21-Day Cycles	Treatment Discontinuation/Early Termination Visit ^d	Follow- Up ^e
			Neoadjuvant Phase Cycles 1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles					Pre- Surgery Visit/ Surgery ^b	Day 1 of Each Cycle (± 3 days)						
	Days –28 to –1	Days –14 to –1	Day 1 of Each Cycle (± 3 days)								Day 1 of Each Cycle (± 3 days)	≤ 30 Days after Final Dose			
			1	2	3	4	5		6	7			8		
Blood sample for WGS or WES			x												
Whole blood sample types for RBR (optional)			x												
Tumor tissue (fresh sample preferred) at screening, on-study, and at time of disease progression or recurrence	See Appendix 3 for detailed schedule.														
Concomitant medications ^{bb}		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events ^{cc}		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Atezolizumab/placebo administration ^{dd}			x	x	x	x	x	x	x	x			x		
Dose-dense doxorubicin administration ^{ee}			x	x	x	x									
Dose-dense cyclophosphamide administration ^{ff}			x	x	x	x									
Pertuzumab administration ^{gg}							x	x	x	x			x		
Trastuzumab administration ^{hh}							x	x	x	x			x		
Paclitaxel administration ⁱⁱ							x	x	x	x					
Trastuzumab emtansine administration ^{kk}													x		

	Screening/ Baseline ^a		Treatment Cycles								Pre- Surgery Visit/ Surgery ^b	Adjuvant Phase ^c (Cycles 9–22) 21-Day Cycles	Treatment Discontinuation/Early Termination Visit ^d	Follow- Up ^e
			Neoadjuvant Phase Cycles 1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles				Day 1 of Each Cycle (± 3 days)							
	Days –28 to –1	Days –14 to –1	Day 1 of Each Cycle (± 3 days)								Day 1 of Each Cycle (± 3 days)	≤ 30 Days after Final Dose		
			1	2	3	4	5	6	7	8				
Survival follow-up and anti-cancer treatment ⁱⁱ													x	

ADA=anti-drug antibody; AJCC=American Joint Committee on Cancer; CT=computed tomography (scan); ddAC=dose-dense anthracycline (doxorubicin)+ cyclophosphamide; ECHO=echocardiogram; eCRF=electronic Case Report Form; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=EuroQol 5-Dimension, 5-Level (questionnaire); FACT-G=Functional Assessment of Cancer Therapy-General; FFPE=formalin-fixed, paraffin-embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; MUGA=multiple-gated acquisition (scan); NAST=neoadjuvant systemic therapy; *pCR*=*pathological complete response*; PK=pharmacokinetic; PRO=patient-reported outcome; Q3W=every 3 weeks; QLQ-C30=Quality of Life Questionnaire-Core 30; RBR=Research Biosample Repository; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WES=whole exome sequencing; WGS=whole genome sequencing.

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

- ^a Results of SOC tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.
- ^b Pre-surgical visit and associated assessments should occur within 14 days of surgery. Surgery should be conducted no earlier than 14 days and no later than 6 weeks after last dose of neoadjuvant therapy. Platelet counts should be checked prior to surgery and should be $\geq 75,000$ cells/ μ L.
- ^c All study therapy will be completed when the patient has received up to a total duration of 52 weeks of HER2-targeted study therapy (neoadjuvant+ adjuvant), regardless of the number of cycles administered.
- ^d Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after their final dose of study treatment.
- ^e The survival follow-up period begins from the date of treatment completion/early termination with a duration of 36 months from the date of the enrollment of the last patient during the global enrollment phase. Follow-up visits will occur every 3 months for 1 year and then every 6 months thereafter until the end of the study. Follow-up visits have a window of ± 28 days.
- ^f 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.

- ^g After signing of the Informed Consent Form, retrieval and submission of tumor tissue sample can occur outside the 28-day screening period. Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). An FFPE block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections should be provided. Fine-needle aspiration is not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. See Section 4.5.9 for additional details.
- ^h Assessment of primary tumor and regional lymph nodes should be done by physical examination at baseline and prior to administration at each cycle of study treatment during neoadjuvant therapy and within 14 days prior to surgery. During the post-operative portion of this study, disease status should be clinically evaluated and documented every 3 months for 2 years, and then every 6 months thereafter until the end of the study. In addition, liver function tests, brain imaging, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease; these assessments should be performed within a timeline as per current local SOC practice. Whenever possible, disease recurrence should be confirmed pathologically. If disease recurrence is diagnosed at any time during the study, patients will discontinue scheduled study assessments and will be followed for survival, anti-cancer medications, and new relapse events. See Section 4.5.5 for additional details.
- ⁱ Baseline tumor staging procedures should be performed in alignment with AJCC, 8th edition (specifically in accordance with Anatomic Stage group rules) at diagnosis, within 28 days of randomization. Tumor size is to be determined via radiologic measurement and node positivity pathologically confirmed by fine needle aspiration or core needle biopsy. See Section 4.5.6 for requirements related to baseline distant sites tumor staging procedures.
- ^j Bilateral mammogram should be obtained within 28 days prior to randomization. Alternatively, provided that the clinical status of the patients has not changed, the screening mammogram can be performed up to 42 days prior to the start of study treatment. Subsequent mammograms are optional during neoadjuvant treatment and prior to surgery and should be performed per investigator's discretion. Bilateral mammogram should occur at study completion/early termination visit and every 12 months (\pm 4 weeks) during the follow-up period. Patients who have undergone mastectomy do not require mammograms on side of mastectomy.
- ^k The patient should be evaluated by a surgeon prior to initiation of neoadjuvant therapy as well as after completion of neoadjuvant therapy/prior to surgery. At baseline, the surgeon should evaluate the patient and create a surgical treatment plan. Then after completion of NAST, the surgeon should reassess the patient and modify the surgical treatment plan as needed.
- ^l Pathological response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines provided in the pathology manual. *Breast cancer surgery and pathological assessment will be performed and reported according to protocol requirements for patients who discontinue study treatment during the neoadjuvant phase (for any reason other than disease progression) and who proceed to surgery without receiving any other non-study anti-cancer therapy prior to surgery. Patients who discontinue neoadjuvant study treatment due to disease progression contribute a non-pCR result and their disease progression must be reported.*

- ^m Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to each infusion and, if clinically indicated, every 15 (\pm 5) minutes during the infusion and at 30 (\pm 10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to each infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during the infusion and at 30 (\pm 10) minutes after the infusion. The vital signs measured prior to the infusion of the first study drug at each cycle are required to be reported on the Vital Sign eCRF. Other vital signs are not required to be entered into the eCRF unless abnormal and clinically significant, in which case they are to be reported as adverse events.
- ⁿ Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. See Section 4.5.3 for additional details. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^o Perform a limited, symptom-directed physical examination at specified timepoints and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^p Refer to Appendix 13.
- ^q Cardiac monitoring (ECHO or MUGA scan) will be performed on all patients enrolled in the study. ECHO/MUGA results need to be reviewed and acted upon as soon as they are available, but study interventions may continue while ECHO/MUGA results are being read assuming that the subject is asymptomatic from a cardiac standpoint. ECHO is the preferred method. The same method used for a given patient at screening should be used throughout the study, unless clinically indicated. ECHO or MUGA scan should be obtained at baseline, after the second dose of ddAC for the cardiac safety cohort (first 26 patients enrolled), after the fourth dose of ddAC (*and prior to Cycle 5, Day 1*), and then every 3 months (\pm 1 week) during study treatment. ECHO or MUGA scan should be obtained at the early termination visit if not performed within the previous 6 weeks. During the survival follow-up period, ECHO or MUGA scan should be obtained every 6 months (\pm 1 week) for the first 2 years and then annually until the end of study. Patients who discontinue study drug(s) for heart failure or LVEF decline should continue to undergo LVEF assessments according to this schedule of activities—irrespective of the initiation of alternative systemic anti-cancer therapy—until resolution, improvement to baseline status, and no further improvement can be expected, or death. Additional ECHO or MUGA scans should be obtained if clinically indicated.
- ^r ECG recordings will be obtained during screening and as clinically indicated at other timepoints. ECGs for each patient should be obtained from the same machine wherever possible. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.
- ^s Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells). Local laboratory assessment can be performed up to 3 days prior to study treatment administration with the option of repeating on the day of study treatment, including the weekly administration of paclitaxel during Cycles 5–8. Local assessment must be reviewed prior to every study treatment administration.
- ^t If screening laboratory assessments were performed within 3 days prior to Day 1 of Cycle 1, they do not have to be repeated.

- ^u Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, and LDH. Local laboratory assessments can be performed up to 3 days prior to study treatment administration with the option of repeating on the day of study treatment, including the weekly administration of paclitaxel during Cycles 5–8. Local assessments must be reviewed prior to every study treatment administration.
- ^v All women of childbearing potential (as defined in Section 4.1.1) will have a serum pregnancy test at screening, within 7 days prior to initiation of study treatment. Urine pregnancy tests will be performed within 24 hours of Day 1 of every cycle until treatment discontinuation. A pregnancy test must be done at the completion/early termination visit, and at 3 months and 7 months after the discontinuation of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- ^w 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.
- ^x Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.
- ^y The PRO assessments (EORTC QLQ-C30, followed by the FACT-G single item GP5, and then the EQ-5D-5L questionnaire) will be completed by the patient 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 the patient's responses. *In scenarios where laboratory assessments (e.g., blood draws) are done in a different clinic than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with patients.* Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. EORTC QLQ-C30 and EQ-5D-5L questionnaires will be completed by patients at baseline (Cycle 1, Day 1) (± 3 days); on Day 1 (± 3 days) of every cycle thereafter until Cycle 8; on Cycle 9, Day 1 (± 3 days); on Day 1 (± 3 days) of every other cycle thereafter until Cycle 22; and at the treatment discontinuation or early termination visit. If cycles are missed or delayed as permitted by the protocol (Appendix 11), the PRO questionnaires should be completed on the day that the patient receives treatment for that cycle, before administration of study treatment. Patients who discontinue study treatment 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 and then every 6 months (± 28 days) thereafter until the end of the study.
- ^z While on study treatment, all patients will complete the FACT-G, single item GP5 beginning on Cycle 2, Day 1 (± 3 days); on Day 1 (± 3 days) of every cycle thereafter until Cycle 8; on Cycle 9, Day 1 (± 3 days); on Day 1 (± 3 days) of every other cycle thereafter until Cycle 22; and at the treatment discontinuation or early termination visit.
- ^{aa} Auto-antibody testing includes anti-nuclear antibody, anti-double-stranded DNA, and circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. The baseline sample will be obtained pre-treatment Cycle 1, Day 1, before the first dose of study drug and stored. For patients who show evidence of immune mediated toxicity, additional samples may be collected and assessed (including the baseline sample) at that time point. All samples will be analyzed centrally.

- ^{bb} 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 30 days prior to initiation of study treatment (for the purposes of screening) until the treatment discontinuation visit. Medication used by the patient within 7 days prior to initiation of study treatment should be recorded. Record all prior anti-cancer therapies, regardless of when they were received.
- ^{cc} 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 systemic 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 systemic anti-cancer therapy, whichever occurs first. After this period, 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). For reporting instructions for deaths, please see Section 5.3.5.8.
- ^{dd} During the neoadjuvant phase, atezolizumab/placebo will be administered by IV infusion at a fixed dose of 840 mg on Day 1 of each 14-day cycle during Cycles 1–4, and 1200 mg on Day 1 of each 21-day cycle during Cycles 5–8. During the adjuvant phase (post-operatively), atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (maximum of 22 cycles [neoadjuvant + adjuvant phases]). Atezolizumab/placebo should be administered as the first infusion. The initial dose of atezolizumab/placebo will be delivered over 60 (\pm 15) minutes. Subsequent infusions will be delivered over 30 (\pm 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (\pm 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. See Section 4.3.2.1 for additional details.
- ^{ee} Doxorubicin 60 mg/m² IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4) according to local practice guidelines. See Section 4.3.2.4 for additional details.
- ^{ff} Cyclophosphamide 600 mg/m² IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4) according to local practice guidelines. See Section 4.3.2.4 for additional details.
- ^{gg} Pertuzumab is given as a fixed non-weight-based dose of 840-mg IV loading dose, then 420 mg IV Q3W. Pertuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. See Section 4.3.2.2 for additional details.
- ^{hh} Trastuzumab is given as an 8-mg/kg IV loading dose, and then 6 mg/kg IV Q3W. Trastuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. See Section 4.3.2.3 for additional details.
- ⁱⁱ Paclitaxel- is given 80 mg/m² IV weekly for 12 continuous weeks (Cycles 5–8) according to local practice guidelines. Chemotherapy should be given after pertuzumab and trastuzumab. See Section 4.3.2.4 for additional details.

- jj After treatment discontinuation, 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 approximately every 3 months for 1 year, then every 6 months until the end of the study (unless the patient withdraws consent or the Sponsor terminates the study). 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 shall use a public information source (e.g., county records) to obtain information about survival status only, where allowable by local regulation.
- kk Trastuzumab emtansine in combination with atezolizumab/placebo (as per randomized therapy) will be an option for patients who did not achieve pCR after completion of neoadjuvant treatment. Trastuzumab emtansine will be given as 3.6 mg/kg IV infusion on Day 1 of a 21-day cycle for a maximum of 14 cycles in the adjuvant setting. See Section 4.3.2.4 for additional details.