Official Title: **A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase II Study Of The Efficacy And Safety Of Trastuzumab Emtansine In Combination With Atezolizumab Or Atezolizumab-Placebo In Patients With HER2-Positive Locally Advanced Or Metastatic Breast Cancer Who Have Received Prior Trastuzumab And Taxane Based Therapy**

NCT Number: NCT02924883

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STATISTICAL ANALYSIS PLAN

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR ATEZOLIZUMAB-PLACEBO IN PATIENTS WITH HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB AND TAXANE BASED THERAPY**
PROTOCOL NUMBER:	WO30085
STUDY DRUG:	Trastuzumab Emtansine (RO5304020) Atezolizumab (RO5541267)
VERSION NUMBER:	1
IND NUMBER:	71,072
EUDRACT NUMBER:	2015-004189-27
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted] Ph.D.
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Name	Reason for Signing	Date and Time (UTC)
	STATISTICAL ANALYSIS PLAN APPROVAL	
[redacted]	Company Signatory	16-Oct-2017 04:50:27

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1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the analyses that are planned to be performed for the Study WO30085 (KATE2). The SAP overrides the analyses described in the statistical section of the protocol.

2. STUDY DESIGN

Study WO30085 is a Phase II, randomized, multicenter, international, two-arm, double-blind, placebo-controlled clinical trial designed to compare the efficacy and safety of trastuzumab emtansine in combination with either atezolizumab or placebo for patients with human epidermal growth factor receptor 2 (HER2)-positive locally advanced or metastatic breast cancer (MBC) who have received prior trastuzumab and taxane based therapy.

Approximately 200 patients will be enrolled in the study at 100 sites worldwide. Patients will be randomized to treatment arms A and B in a 1:2 ratio by means of a permuted block randomization scheme through the use of an interactive Web or voice response system (IxRS). Randomization will be stratified according to 1) tumor programmed death–ligand 1 (PD-L1) status (IC[1]0 vs IC1/2/3), 2) World Region (Western Europe vs U.S. vs Rest of World) and 3) Presence of liver metastases (yes vs. no).

Patients will be treated in one of the following arms:

- Arm A: trastuzumab emtansine 3.6 mg/kg and placebo, every 3 weeks (q3w) (approximately 67 patients)
- Arm B: trastuzumab emtansine 3.6 mg/kg and atezolizumab 1200 mg, q3w (approximately 133 patients)

Arm A and Arm B will be blinded with respect to administration of atezolizumab or placebo. Cross-over between treatment arms will not be permitted.

The study schema can be found in the protocol.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2 to Appendix 4.

2.2 ENDPOINTS

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

[1] IC = tumor-infiltrating immune cells

2.3 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint for this study is progression-free survival (PFS) based on investigator tumor assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The primary analysis for PFS will be performed when approximately 115 PFS events have occurred.

With approximately 200 patients randomized according to a 1:2 randomization (approximately 67 patients will be randomized to the trastuzumab emtansine plus placebo arm and approximately 133 patients will be randomized to the trastuzumab emtansine plus atezolizumab arm) the study has the estimated power for the PFS hazard ratios (HRs) presented in Table 1.

Table 1 Estimated Power at Primary PFS Analysis for Different PFS HRs

PFS HR	Estimated power for log-rank test
0.50	94%
0.55	86%
0.60	73%
0.65	58%

HR = Hazard ratio; PFS = progressive-free survival.
Estimated power figures calculated using a 2-sided log-rank test at 0.05 alpha level when 115 PFS events have been observed, assuming a median PFS of 6.2 months for trastuzumab emtansine plus placebo.

The above study design considerations assume proportional hazards, a cumulative dropout rate of 10% in each treatment arm and an estimated recruitment time of about 9 months (with ramp up in the first 4 months). The estimated time from first patient in (FPI) to primary PFS analysis is 15 to 17 months, depending on PFS HR assumption.

Sample size and power calculations were performed using the East 6 software package (Cytel Inc.).

2.4 ANALYSIS TIMING

The primary PFS analysis will be performed when approximately 115 investigator-assessed PFS events have been observed which is anticipated to occur approximately 15 to 17 months from first patient enrolled (FPI), depending on PFS HR assumptions.

The first analysis of overall survival (OS) will be performed at the time of the primary PFS analysis. Another update for OS will be performed at approximately 12 months after the primary PFS analysis. The final OS analysis will be performed at approximately 24 months after the primary PFS analysis or when ~50% OS events from 200 patients can be obtained, whichever occurs first. The Sponsor may consider additional OS

updates beyond 24 months after primary PFS analysis if more mature OS data are requested by the Health Authority.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients will be randomized in a 1:2 ratio to either the trastuzumab emtansine plus placebo arm or the trastuzumab emtansine plus atezolizumab arm. A permuted block randomization scheme will be used to achieve balance in treatment assignment within the two treatment arms with respect to the following stratification factors:

- PD-L1 Status (PD-L1 IC 0 vs. IC 1/2/3)
- World Region (Western Europe vs U.S. vs. Rest of World)
- Liver Metastases (Yes vs. No)

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) composed of a group of independent experts external to the Sponsor, with the aid of an independent Data Coordinating Center (iDCC), will monitor patient safety data in an unblinded fashion during the course of the study. Details of the committee's composition, meeting timelines, and the members' roles and responsibilities are specified in the iDMC Charter.

4. STATISTICAL METHODS

The analyses outlined in this SAP supersede those specified in the protocol.

4.1 ANALYSIS POPULATIONS

4.1.1 Intention-to-Treat Population

The intention-to-treat (ITT) population includes all patients who are randomized to the study, whether or not they receive any study drug. Patients will be grouped according to the treatment assigned at randomization by the IxRS. The ITT population is the analysis population for all efficacy endpoints.

4.1.2 Safety Population

The safety analysis population includes all randomized patients who receive at least one full or partial dose of study drug, with patients grouped according to the treatment received. Patients who received any amount of atezolizumab will be included in the atezolizumab treatment arm; all other treated patients will be included in the control arm.

4.2 ANALYSIS OF STUDY CONDUCT

Patient enrollment, duration of follow-up, discontinuation from treatment and from study, and discontinuation reasons will be descriptively summarized by treatment arm. In addition, protocol violations will be summarized by treatment arm.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment arm comparability will include summaries of demographics, breast cancer (BC) history, baseline disease characteristics, patient treatment history, and a summary of randomization stratification factors.

Descriptive statistics (mean, median, SD, 25th percentile, 75th percentile, and range) will be presented by treatment arm for continuous variables such as age or time since initial BC diagnosis. Frequency counts will be presented by treatment arm for categorical variables such as gender, race, and age category.

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

4.4 EFFICACY ANALYSIS

All efficacy analyses will be performed based on the ITT population.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is PFS based on investigator tumor assessment per RECIST v1.1.

Progression-free survival is defined as the time from randomization to first documented disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs earlier. Data for patients without disease progression or death from any cause as of the data cutoff date will be censored at the time of the last tumor assessment with an outcome other than “unevaluable” (or, if no tumor assessment was performed after the baseline visit, will be censored at the time of randomization plus one day). Data from patients who are lost to follow-up will be included in the analysis as censored observations on the date of the last tumor assessment that the patient was known to be progression-free. When disease progression or death occurs after two or more consecutive missed (or “unevaluable”) tumor assessments, these events will not be counted; rather, the patient will be censored at the patient’s last tumor assessment prior to the first missing (or “unevaluable”) assessment. If disease progression or death occurs after one missed (or “unevaluable”) tumor assessment, the event will be counted at the respective event date.

The Kaplan-Meier method will be used to estimate median PFS and the corresponding 95% CIs for each treatment arm. The 2-sided log-rank test, stratified by world region (Western Europe vs U.S. vs Rest of World) and PD-L1 status (IC 0 vs IC 1/2/3), based on data collected by the IxRS, will be used to compare PFS between treatment arms at the overall two-sided significance level of 5%. Liver metastases will be excluded because of the potential that some of the strata may have very few patients, which would result in a loss of power. Results from an unstratified analysis and a stratified analysis with stratification factors collected on the electronic Case Report Form (eCRF) will also be provided. The Cox proportional hazards model, stratified by the previous noted

stratification factors, excluding liver metastases, will be used to estimate the HR and to calculate the 95% CI of the HR.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Overall Survival

Overall survival is defined as the time from randomization to the date of death from any cause. Patients who are alive as of the data cutoff date for the analysis will be censored at the last known date they were alive. Patients with no post-baseline information will be censored at the date of randomization plus one day. The Kaplan-Meier method will be used to estimate median OS and the corresponding 95% CIs for each treatment arm. The 2-sided log-rank test, stratified by world region (Western Europe vs U.S. vs Rest of World) and PD-L1 status (IC 0 vs IC 1/2/3), will be used to compare OS between treatment arms. The unstratified log-rank test result will also be provided. The Cox proportional hazards model, stratified by the previous noted stratification factors, excluding liver metastases, will be used to estimate the HR and to calculate the 95% CI of the HR.

4.4.2.2 Objective Response

Objective response, defined as a complete response (CR) or partial response (PR), will be determined by investigator tumor assessment using RECIST v1.1. Only patients with measurable disease at baseline will be included in the analysis of objective response. Objective response rate (ORR) is the percentage of patients who are determined to have an objective response. Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified by world region (Western Europe vs U.S. vs Rest of World) and PD-L1 status (IC 0 vs IC 1/2/3) will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

4.4.2.3 Duration of Response

Only patients with an objective response will be included in the analysis of duration of response (DOR). Duration of response is defined as the time from first occurrence of a documented objective response (PR or CR) to disease progression, as determined by investigator tumor assessment using RECIST v1.1, or death from any cause, whichever occurs first. The Kaplan-Meier approach will be used to estimate the median DOR and the corresponding 95% CIs for each treatment arm. The stratified Cox proportional hazards model, stratified by world region (Western Europe vs U.S. vs Rest of World) and PD-L1 status (IC 0 vs IC 1/2/3), will be used to estimate the HR and to calculate the 95% CI of the HR. Because of the non-randomized nature of the subgroup of patients who achieve an objective response, the analysis of DOR will be considered descriptive.

4.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be evaluated at time of primary efficacy analysis.

4.4.3.1 Progression-Free Survival Assessed in the PD-L1 Selected Subgroup

Progression-free survival, defined as the time from randomization to first occurrence of disease progression, will be determined by investigator assessment using RECIST v1.1 or death from any cause, whichever occurs earlier, in the PD-L1 selected subgroup of patients defined as having tumor immune infiltrating cell expression of IC 1/2/3, as assessed by immunohistochemistry (IHC). The analysis methods are similar to those described for the primary efficacy endpoint.

4.4.3.2 Progression-Free Survival Assessed Using Immune-Modified RECIST

Progression-free survival, defined as the time from randomization to first occurrence of disease progression, will be determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs earlier. The analysis methods are similar to those described for the primary efficacy endpoint.

4.4.3.3 Objective Response Based on Immune-Modified RECIST

Objective response, defined as a CR or PR, will be determined by investigator tumor assessment using immune-modified RECIST. Only patients with measurable disease at baseline will be included in the analysis of objective response. Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. The analysis methods are similar to those described for the secondary efficacy endpoint ORR.

4.4.3.4 Duration of Response Based on Immune-Modified RECIST

Duration of response, defined as the time from first occurrence of a documented objective response (PR or CR) to disease progression, will be determined by investigator tumor assessment using immune-modified RECIST, or death from any cause, whichever occurs first. The analysis methods are similar to those described for the secondary efficacy endpoint DOR.

4.4.3.5 One-Year Survival Rate

Kaplan-Meier methodology will be used to estimate one-year survival rates and 95% CIs for each treatment arm. Also, differences in one-year survival rates between treatment arms will be calculated together with 95% CIs. The p-value and the 95% CI will be computed using Greenwood's estimate of the standard error.

4.4.4 Sensitivity Analyses

Censoring for non-protocol therapy

Non-protocol therapy (NPT) is defined as any anti-cancer therapy other than study treatment the patient receives that is intended to treat his or her metastatic breast cancer (MBC) prior to documented disease progression. The impact of NPT on the primary endpoint of investigator-assessed PFS by RECIST v1.1 will be evaluated. A sensitivity analysis will be performed in which data for patients who received NPT will be censored at the last tumor assessment date before the patient received NPT.

Missed Tumor Assessments

A sensitivity analysis will be performed on the primary endpoint of PFS. Specifically, if a patient has a documented progression after two or more missing or unevaluable assessments, the patient's progression event will still be recorded as an event at the documented progression date.

Additional sensitivity analyses may be considered if appropriate.

4.4.5 Subgroup Analyses

In order to assess the consistency of treatment benefit with respect to the primary efficacy endpoint PFS across important subgroups, forest plots (including estimated HRs) will be provided for the following variables:

- Race
- Age ($<$65 years and $\geq$65 years)
- World region
- Baseline PD-L1 expression
- Liver metastases
- Eastern Cooperative Oncology Group (ECOG) status
- Hormone receptor status
- Visceral disease
- The number of lines of prior therapy for locally advanced or metastatic disease.

Visceral disease is defined as the presence of disease in the lung, liver, adrenal gland, central nervous system, pleural cavity or peritoneal cavity. Additional variables may be considered if necessary. A multivariate Cox regression analysis will be performed on the primary efficacy endpoint of investigator-assessed PFS controlling for important baseline characteristics.

4.5 PHARMACOKINETIC ANALYSES

The pharmacokinetic (PK) analyses will include patients with at least one post-dose PK assessment. Individual serum atezolizumab, trastuzumab emtansine, total trastuzumab levels and plasma DM1 concentrations versus time will be tabulated and summarized by treatment arm and study visit day. Descriptive statistics will include mean, median,

range, SD, coefficient of variation (CV%), geometric mean, and geometric mean coefficient of variation (CVb%) as appropriate. The pharmacokinetics of atezolizumab in the presence of trastuzumab emtansine will be assessed. The pharmacokinetics of trastuzumab emtansine in the presence and absence of atezolizumab will be assessed and compared.

Additional exploratory PK/PD analyses may be conducted if deemed appropriate.

4.6 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will be conducted for both trastuzumab emtansine and atezolizumab, and include patients with at least one predose and one post-dose anti-therapeutic antibody (ATA) assessment, with patients grouped according to treatment received. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA-positive if they are ATA-negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA-positive at baseline and the titer of one or more post-baseline samples is at least four-fold greater (i.e.,$\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA-negative if they are ATA-negative at baseline and all post-baseline samples are negative, or if they are ATA-positive at baseline but do not have any post-baseline samples with a titer that is at least four-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy may also be evaluated if appropriate.

4.7 BIOMARKER ANALYSES

Baseline biomarker expression levels will be summarized by treatment arm. Descriptive statistics (mean, median, SD and range) will be presented for continuous biomarker data. Frequency counts will be presented for categorical biomarker data.

Exploratory biomarker analyses will be performed in an effort to understand the association with study drug response, including efficacy. Due to the availability of samples, only biomarkers in tumor tissue samples will be analyzed at the time of primary analysis, including:

- PD-L1 IHC status
- HER2 expression level
- CD8/PanCK IHC expression
- Immune or cancer-related gene signatures
- PIK3CA mutation status
- Tumor mutational burden (TMB)

4.8 SAFETY ANALYSES

Safety analyses will be performed based on the safety analysis population.

4.8.1 Exposure to Study Drug

The number of patients who experience any dose modification (including dose delay, dose reduction and dose interruption) or dose discontinuation will be summarized for each of the treatment arm regimens. In addition, the number of patients that discontinue from trastuzumab emtansine and/or atezolizumab/placebo because of toxicity will be summarized.

Descriptive statistics will be presented for total cumulative dose, number of cycles, dose intensity, and weeks of exposure for trastuzumab emtansine, and atezolizumab.

4.8.2 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. The following events occurring on or after the first dose of study drug (i.e., treatment-emergent AEs) will be summarized by NCI CTCAE v4.03 grade:

- All AEs
- Serious adverse events
- AEs leading to death
- AEs leading to study drug discontinuation
- AEs leading to dose reduction and interruption

For events of varying severity, the highest grade will be used in the summaries.

Deaths and causes of death will be summarized. Selected AEs will be summarized by NCI CTCAE v4.03 grade for each treatment arm based on pre-specified category definitions, including (but not limited to) hepatotoxicity, cardiac dysfunction, thrombocytopenia, infusion-related reactions/hypersensitivity, pulmonary toxicity, peripheral neuropathy, hemorrhage, and immune-related AEs associated with atezolizumab, including but not limited to hepatitis (diagnosis and laboratory abnormal), hypothyroidism, hyperthyroidism, adrenal insufficiency, pneumonitis, colitis, Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis, pancreatitis, diabetes mellitus, myositis, nephritis, rash, rhabdomyolysis, systemic immune activation, meningitis, encephalitis, ocular inflammatory toxicity, vasculitis, hypophysitis, myocarditis, severe cutaneous reaction and hemolytic anemia. Additional analyses may be performed as indicated.

4.8.3 Laboratory Data

For laboratory parameters, descriptive summary tables of change from baseline over time based on System International (SI) units will be produced. Summary tables for laboratory abnormality and the shifts in NCI CTCAE v4.03 grades from baseline to the worst post-baseline value will be presented.

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

4.8.4 Vital Signs

Vital signs will be summarized descriptively over time including change from baseline.

4.8.5 Left Ventricular Ejection Fraction Assessments

The number of patients with a drop in Left Ventricular Ejection Fraction (LVEF) of ≥ 10 ejection fraction points from baseline to a LVEF$<$50% will be summarized. The maximum decrease in LVEF from baseline will be summarized by treatment arm. In addition, the lowest available ejection fraction measurements at any time on the study and the lowest post-baseline value from each patient will be summarized. Further analyses will be performed if indicated by the data.

4.9 MISSING DATA

For the analyses of PFS and DOR, data for patients without disease progression or death from any cause as of the data cutoff date will be censored at the time of the last tumor assessment with an outcome other than "unevaluable" (or, if no tumor assessment was performed after the baseline visit, will be censored at the time of randomization plus one day). Data from patients who are lost to follow-up will be included in the analyses as censored observations on the date of the last tumor assessment that the patient was known to be progression-free. When disease progression or death occurs after two or more consecutive missed (or "unevaluable") tumor assessments, these events will not be counted; rather, the patient will be censored at the patient's last tumor assessment prior to the first missing (or "unevaluable") assessment. If disease progression or death occurs after one missed (or "unevaluable") tumor assessment, the event will be counted at the respective event date.

For the analysis of OS, patients who are alive as of the data cutoff date for the analysis will be censored at the last known date they were alive. Patients with no post-baseline information will be censored at the date of randomization plus one day.

For the analysis of ORR, patients without a post-baseline tumor assessment will be considered non-responders.

4.10 INTERIM ANALYSES

There is no planned interim efficacy analysis for PFS.

Appendix 1
Protocol Synopsis

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR ATEZOLIZUMAB-PLACEBO IN PATIENTS WITH HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB AND TAXANE BASED THERAPY**
PROTOCOL NUMBER:	WO30085
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2015-004189-27
IND NUMBER:	71,072
TEST PRODUCT:	Trastuzumab Emtansine (RO5304020) Atezolizumab (RO5541267)
PHASE:	Phase II
INDICATION:	Locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of trastuzumab emtansine in combination with atezolizumab or placebo (atezolizumab-placebo) in patients with human epidermal growth factor 2 (HER2)-positive, locally advanced or metastatic breast cancer (MBC), who have received prior trastuzumab and taxane based therapy, either alone or in combination, and/or who have progressed within 6 months after completing adjuvant therapy. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of the combination of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo on the basis of the following endpoint:

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

Secondary Efficacy Objective

The secondary efficacy objectives for this study are to evaluate the efficacy of the combination of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Overall survival (OS), defined as the time from randomization to death from any cause
- Objective response, defined as a complete response (CR) or partial response (PR) on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

- Duration of objective response, defined as the time from first occurrence of a documented objective response to disease progression, as determined by investigator assessment using RECIST v1.1 or death from any cause, whichever occurs first

Exploratory Efficacy Objective

The exploratory efficacy objectives for this study are to evaluate the efficacy of the combination of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator assessment using RECIST v1.1 or death from any cause, whichever occurs first, in the programmed death–ligand 1 (PD-L1) selected subgroup of patients defined as having tumor immune infiltrating cell (IC) expression of IC 1/2/3, as assessed by immunohistochemistry
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs first
- Objective response, defined as a CR or PR on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using immune modified RECIST
- Duration of objective response, defined as the time from first occurrence of a documented objective response to disease progression, as determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs first
- 1-year survival rate

Safety Objective

The primary safety objectives for this study are to evaluate the overall safety of trastuzumab emtansine in combination with atezolizumab compared with trastuzumab emtansine in combination with placebo on the basis of the following:

- Nature, frequency, severity, and timing of adverse events including cardiac, hepatic and pulmonary events
- Clinical laboratory results during and following trastuzumab emtansine and atezolizumab administration

Pharmacokinetic Objective

The secondary pharmacokinetic (PK) objectives for this study are:

- To characterize the pharmacokinetics of atezolizumab in the presence of trastuzumab emtansine
- To characterize the pharmacokinetics of trastuzumab emtansine in the presence and absence of atezolizumab

Immunogenicity Objective

The secondary immunogenicity objectives for this study are:

- To characterize the incidence of anti-therapeutic antibody (ATA) to atezolizumab in the presence of trastuzumab emtansine
- To characterize the incidence of ATA to trastuzumab emtansine in the presence and absence of atezolizumab

The exploratory immunogenicity objectives for this study are as follows:

- To evaluate the relationship between ATA status, efficacy, safety, and/or pharmacokinetics

Biomarker Objective

- To assess if baseline PD-L1 expression is associated with efficacy
- To assess if baseline immune status is associated with efficacy
- To assess if baseline immune status together with HER2 expression level (mRNA, protein and/or gene copy number/ratio) are associated with efficacy
- To assess changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with atezolizumab in combination with trastuzumab emtansine

- To evaluate the relationship between tumor biomarkers and efficacy
- To identify candidate biomarkers that correlate with safety signals

Study Design

Description of Study

This is a Phase II, randomized, multicenter, international, two-arm, double-blind, placebo-controlled clinical trial designed to compare the efficacy and safety of trastuzumab emtansine in combination with either atezolizumab or placebo for patients with HER2-positive locally advanced or MBC who have received prior trastuzumab and taxane based therapy.

Approximately 200 patients will be enrolled in the study at 100 sites worldwide. Patients will be randomized to treatment arms A and B in a 1:2 ratio by means of a permuted block randomization scheme through the use of an interactive Web or voice response system. Randomization will be stratified according to 1) PD-L1 status (IC0 vs IC1/2/3), 2) World Region (Western Europe vs U.S. vs Rest of World) and 3) Presence of liver metastases (yes vs. no).

Patients will be treated in one of the following arms:

- Arm A: trastuzumab emtansine 3.6 mg/kg and placebo, every 3 weeks (q3w) (approximately 67 patients)
- Arm B: trastuzumab emtansine 3.6 mg/kg and atezolizumab 1200 mg, q3w (approximately 133 patients)

Arm A and Arm B will be blinded with respect to administration of atezolizumab or placebo. Cross-over between treatment arms will not be permitted.

Number of Patients

Approximately 200 patients will be enrolled in the study and randomized to treatment arms A and B in a 1:2 ratio (approximately 67 patients in Arm A and 133 patients in Arm B).

Target Population

Inclusion Criteria

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

- Age $\geq$ 18 years.
- Signed written informed consent approved by the institution's Independent Ethical Committee/Institutional Review Board.
- Archival tumor samples must be obtained from primary and/or metastatic sites. Representative FFPE tumor specimens in paraffin blocks for central testing is required. Different material as described in Appendix 3 may be accepted in exceptional cases. Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated for HER2 and PD-L1 expression prior to enrollment.
- Patients must submit tumor tissue that is evaluable for PD-L1 expression to be eligible for this study. If multiple tumor specimens are submitted (e.g., an archival specimen [from initial BC diagnosis] and tissue from metastatic or locally advanced breast cancer [LABC] disease), patients may be eligible if at least one specimen is evaluable for PD-L1.

  For the purpose of stratification, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.
- HER2-positive breast cancer (BC) as defined by an immunohistochemistry (IHC) score of 3+ or gene amplified by in situ hybridization (ISH) as defined by a ratio of $\geq$ 2.0 for the number of HER2 gene copies to the number of chromosome 17 copies, prospectively tested by a Sponsor- designated central laboratory prior to enrollment. Both IHC and ISH assays will be performed; however, only one positive result is required for eligibility.

If multiple tumor specimens are submitted, the HER2 IHC score and or ISH amplification ratio will first be assessed on the archival specimen for the purpose of determining eligibility. For patients with bilateral BC, HER2 positivity must be demonstrated in both locations for archival tissue or in a metastatic biopsy.

Centrally confirmed HER2 results (either IHC or ISH) from a current or previous Sponsor study can be used to determine eligibility for this study. Approval must be obtained from the Medical Monitor prior to randomization.

Progression must have occurred during or after most recent treatment for LABC or MBC or within 6 months after completing adjuvant therapy.

- Histologically or cytologically confirmed invasive BC: incurable, unresectable, locally advanced BC previously treated with multimodality therapy or MBC.
- Prior treatment for BC in the: adjuvant; unresectable locally advanced; or metastatic settings; which must include both, a taxane and trastuzumab (alone or in combination with another agent)
- Progression must have occurred during or after most recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy.
- Patients must have measurable disease that is evaluable per RECIST 1.1.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):

  Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte-colony stimulating factor [support) within 7 days prior to Cycle 1, Day 1

  Platelet count $\geq 100{,}000/\mu$L (without transfusion within 7 days prior to Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL

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

  Albumin > 2.5g/dL

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

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

  Total bilirubin $\leq 1.5 \times$ the ULN

  INR and aPTT $\leq 1.5 \times$ the ULN

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

  Calculated creatinine clearance ≥ 30 mL/min
- Negative serum pregnancy test within 7 days of enrollment for pre-menopausal women and for women less than 12 months after the onset of menopause.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine, or 5 months after the last dose of atezolizumab/placebo, whichever is later.

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence

(e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose trastuzumab emtansine. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine 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.

Exclusion Criteria

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

- Prior treatment with trastuzumab emtansine, CD137 agonists, anti- programmed death−1 (PD-1), or anti-PD-L1 therapeutic antibody or pathway−targeting agents.
- Receipt of any anti-cancer drug/biologic or investigational treatment 21 days prior to Cycle 1 Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1 Day 1; recovery of treatment-related toxicity consistent with other eligibility criteria.
- Radiation therapy within 2 weeks prior to Cycle 1, Day 1

  The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines as specified below:

  Doxorubicin > 500 mg/m^2

  Liposomal doxorubicin > 500 mg/m^2

  Epirubucin > 720 mg/m^2

  Mitoxantrone > 120 mg/m^2

  Idarubicin > 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence.
- Cardiopulmonary dysfunction as defined by:

  Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg)

  Inadequate left ventricular ejection function at baseline, $< 50\%$ by either ECHO or MUGA

  History of symptomatic congestive heart failure (CHF)-Grade ≥ 3 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or Class $\geq$ II New York Health Association

  History of a decrease in left ventricular ejection function to $< 40\%$ or symptomatic CHF with prior trastuzumab treatment

  Myocardial infarction or unstable angina within 6 months of randomization

  Current dyspnoea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy

  Serious cardiac arrhythmia not controlled by adequate medication

- Patients with severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures).
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment.
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis or active infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)

  Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or HCV antibody. HIV, HBV, or HCV assessments are required at screening.

  Patients who test positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV DNA.

  Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.
- Need for current chronic corticosteroid therapy ($\geq$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)

  Stable use (i.e., no change in dose within 3 months prior to Cycle 1, Day 1) of inhaled corticosteroids is allowed.
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $>$ 2 weeks prior to randomization.
- Patients with known central nervous system (CNS) disease are not eligible, except for treated asymptomatic CNS metastases, provided that all of the following criteria are met:

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

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 14 days prior to randomization

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
- Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Leptomeningeal disease
- Symptomatic pleural effusion, pericardial effusion, or ascites.
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium or calcium $>$ 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.

  Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade $\geq$ 3 peripheral neuropathy (according to the NCI CTCAE v4.0).
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins.

- History of autoimmune disease, including, but not limited to, myasthenia gravis, autoimmune myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

    Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.

    History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis).

    Patients with Type 1 diabetes mellitus will not be eligible unless controlled with the patient on a stable insulin regimen

    Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are excluded unless they meet the following conditions:

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

        Disease is well controlled at baseline and requiring only low-potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

        No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet. A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral steroids)

        Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.
- Prior allogeneic stem cell or solid organ transplantation.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography scan.

    Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.
- Active tuberculosis.
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study.
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization.
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the trial.

    Patients who need current chronic corticosteroid therapy (≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids) will be excluded

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

    Stable use (i.e., no change in dose within 3 months prior to Cycle 1, Day 1) of inhaled corticosteroids is allowed
- Breastfeeding, or intending to become pregnant during the study

End of Study

The end of study is triggered by the final OS analysis following last patient last visit *that* is planned to occur approximately *24* months after the primary efficacy analysis *or at approximately 50% OS events from 200 patients can be obtained, whichever occurs first. The Sponsor may consider additional OS update(s) beyond 24 months after primary PFS*

analysis if more mature OS data are requested by the Health Authority. The Sponsor may also terminate the study at any time.

Length of Study

The total duration of the study is expected to be approximately *40* months.

Investigational Medicinal Products

Trastuzumab emtansine, atezolizumab, and placebo are investigational medicinal products for this study.

Test Product (Investigational Drug)

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by intravenous (IV) infusion, q3w. The dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes ≥ 10% compared to the previous visit or baseline. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed. Once a dose has been reduced for adverse event(s), it must not be re-escalated. If trastuzumab emtansine is discontinued because of toxicity, it should not be re-administered.

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, on the earliest following date with subsequent protocol-specified procedures rescheduled accordingly.

Patients will receive 1200 mg of atezolizumab/placebo administered by IV infusion q3w.

Both trastuzumab emtansine and atezolizumab/placebo 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.

All the study drugs are to be administered to patients intravenously. Atezolizumab or placebo will be administered first, followed by trastuzumab emtansine.

Statistical Methods

Primary Efficacy Analysis

The primary efficacy endpoint for this study is PFS based on investigator tumor assessment. The intention-to-treat (ITT) population is the primary analysis population for the primary efficacy endpoint and includes all patients who are randomized to the study, whether or not they receive any study medication. *Treatment group for the ITT population will be defined according to the treatment assigned at randomization.*

PFS is defined as the time from randomization to first documented disease progression as determined by the investigator using RECIST 1.1 or death from any cause, whichever occurs earlier. The first documented disease progression will be used in the main analysis of the primary efficacy endpoint of PFS. Data for patients without disease progression or death from any cause as of the data cut-off date will be censored at the time of the last tumor assessment with an outcome other than "unevaluable" (or, if no tumor assessment was performed after the baseline visit, at the time of randomization plus 1 day). Data from patients who are lost to follow-up will be included in the analysis as censored observations on the date of the last tumor assessment that the patient was known to be progression-free. When disease progression or death occurs after two or more consecutive missed (or "unevaluable") tumor assessments, these events will not be counted; rather, the patient will be censored at the patient's last tumor assessment prior to the first missing (or "unevaluable") assessment. If disease progression or death occurs after one missed (or "unevaluable") tumor assessment, the event will be counted at the respective event date.

The Kaplan-Meier method will be used to estimate median PFS and the corresponding 95% confidence intervals (CIs) for each treatment arm. The 2-sided log-rank test, stratified by the factors specified in the protocol (excluding liver metastases), will be used to compare PFS between the treatment arms at the overall two-sided significance level of 5%. Liver metastases will be excluded because of the potential that some of the strata may have very few patients, which would result in a loss of power. The stratification factors will be based on data collected by the IxRS rather than on data collected on the eCRFs. The unstratified log-rank test result will also be provided. The Cox proportional hazards model, stratified by

the previous noted stratification factors, excluding liver metastases, will be used to estimate the HR and to calculate the 95% CI of the HR.

The *primary* PFS analysis will be performed when approximately *115* investigator-assessed PFS events have been observed and is anticipated to occur approximately *15 to 17* months from *first patient enrolled (*FPI*)*, depending on PFS HR assumptions.

Several sensitivity analyses will be performed to assess the robustness of the primary efficacy analysis, see the SAP for details.

In order to assess the consistency of treatment benefit with respect to the primary efficacy endpoint PFS across important subgroups, forest plots (including estimated HRs) will be provided, including, but not limited, to the following variables: race, age, sex, world region, baseline PD-L1 expression, ECOG status and hormone receptor status. A multivariate Cox regression analysis will be performed on the primary efficacy endpoint of investigator-assessed PFS controlling for important baseline characteristics.

Secondary Efficacy Analysis

The ITT population will be the analysis population used for evaluation of the secondary efficacy endpoints.

Overall Survival

OS is defined as the time from randomization to death from any cause. Patients who are alive as of the data cut-off date of the analysis will be censored at the last known date they were alive. Patients with no post-baseline information will be censored at the date of randomization plus 1 day. Methods for data analysis are analogous to those described for the primary efficacy endpoint.

The first analysis of OS will be performed at the time of the primary PFS analysis. Another update for OS will be performed at approximately 12 months after the primary PFS analysis. The final OS analysis will be performed at approximately 24 months after the primary PFS analysis or when ~50% OS events from 200 patients can be obtained, whichever occurs first. The Sponsor may consider additional OS updates beyond 24 months after primary PFS analysis if more mature OS data are requested by the Health Authority.

Objective Response Rate

Objective response, defined as a CR or PR, will be determined by investigator tumor assessment using RECIST 1.1. *Only patients with measurable disease at baseline will be included in the analysis of objective response.* Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the objective response rate (ORR) and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified according to the factors *specified in the protocol (excluding liver metastases)* will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

Duration of Response

DOR is defined as the time from first occurrence of a documented objective response (PR or CR) to disease progression, as determined by investigator tumor assessment using RECIST 1.1, or death from any cause, whichever occurs first. The analysis methods are similar to those described for the primary efficacy endpoint PFS. The limitations of this responder analysis are acknowledged.

Exploratory Efficacy Analysis

The exploratory efficacy endpoints will be evaluated at time of primary efficacy analysis. The ITT population will be the analysis population used for evaluation of the exploratory efficacy endpoints.

PFS Assessed in the PD-L1 Selected Subgroup

The analysis methods are similar to those described for the primary efficacy endpoint.

PFS Assessed Using Immune-Modified RECIST

PFS is defined as the time from randomization to first occurrence of disease progression as determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs earlier. Only patients who are clinically eligible for treatment beyond disease progression will be included in this analysis. The analysis methods are similar to those described for the primary efficacy endpoint.

Objective Response Rate based on Immune Modified RECIST

Objective response, defined as a complete response (CR) or partial response (PR), will be determined by investigator tumor assessment using immune-modified RECIST. Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified *according to the factors specified in the protocol (excluding liver metastases)* will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

Duration of Response *based on Immune-Modified RECIST*

DOR is defined as the time from first occurrence of a documented objective response (PR or CR) to disease progression, as determined by investigator tumor assessment using immune-modified RECIST, or death from any cause, whichever occurs first. The analysis methods are similar to those described for the primary efficacy endpoint PFS.

1-Year Survival Rate

Kaplan-Meier methodology will be used to estimate 1-year survival rates and 95% CIs for each treatment arm. Also, differences in 1-year survival rates between treatment arms will be calculated together with 95% CIs.

Safety Analysis

The safety analysis population will include all randomized patients who received at least one full or partial dose of study drug. Safety analyses will be performed based on the treatment the patient actually received.

Study Drug Exposure

The number of patients who experience any dose modification (including dose delay, dose reduction and dose interruption), or dose discontinuation, and reasons for study treatment discontinuation will be summarized for each of the treatment arm regimens. In addition, the number of patients that discontinue from trastuzumab emtansine-containing and/or atezolizumab-containing treatment because of toxicity and/or receive other non-protocol anti-cancer therapy will be summarized.

Descriptive statistics will be presented for total cumulative dose, number of cycles, dose intensity, infusion time by cycle, and weeks of exposure for trastuzumab emtansine, and atezolizumab.

Adverse Events

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, study treatment exposures, and immunogenicity as measured by ATA and will be presented by treatment arm.

Verbatim descriptions of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the NCI CTCAE v4.0. The following events occurring on or after the first dose of study drug (i.e., treatment-emergent adverse events) will be summarized by NCI CTCAE grade:

- All adverse events
- Serious adverse events
- Adverse eventsleading to death
- Adverse eventsleading to study drug discontinuation

- Adverse eventsleading to dose reduction
- *Sponsor-defined adverse events of special interest*

For events of varying severity, the highest grade will be used in the summaries.

Deaths and causes of death will be summarized. Selected adverse events will be summarized by NCI CTCAE grade for each treatment arm based on pre-specified category definitions, including (but not limited to) hepatotoxicity, cardiac dysfunction, and thrombocytopenia. In addition, adverse eventsoccurring within 1 day (24 hours) of the first dose of each treatment cycle will be summarized to help characterize potential infusion-related reactions.

Additional *safety* analyses may be performed as indicated.

Laboratory Data

For laboratory parameters, descriptive summary tables of change from baseline over time based on System International units will be produced. Summary tables for the shifts in NCI CTCAE v4.0 grades from baseline to the worst grade observed during treatment will be presented.

Pharmacokinetic Analysis

The PK analyses will include patients with at least one post-dose PK assessment.

Individual serum atezolizumab, trastuzumab emtansine, total trastuzumab levels and plasma DM1 concentrations versus time will be tabulated and summarized by treatment arm and study visit day. Descriptive statistics will include mean, medians range, standard deviation, coefficient of variation (CV%), geometric mean, and geometric mean coefficient of variation (CVb%) as appropriate.

Additional PK and PD analyses will be conducted as appropriate.

Immunogenicity Analysis

The immunogenicity analyses will include patients with at least one predose and one post-dose ATA assessment, with patients grouped according to treatment received. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

Biomarker Analysis

Descriptive statistics will be utilized for the analysis and reporting of the exploratory biomarker objectives. This may include appropriate multivariate analyses.

Determination of Sample Size

The primary efficacy endpoint for this study is PFS based on investigator tumor assessment. *The primary PFS analysis will be performed when approamiately 115 PFS events have occurred.*

With approximately 200 patients randomized according to a *1:2* randomization (approximately *67* patients will be randomized to Arm A and approximately *133* patients will be randomized to Arm B) the study has the estimated power for the PFS HRs. The design considerations assumed proportional hazards, a cumulative dropout rate of 10% in each treatment arm and result in an estimated recruitment time of about 9 months (with ramp up in the first 4 months). The estimated time from FPI to *primary* PFS analysis is *15 to 17* months, depending on PFS HR assumption.

Sample size and power calculations were performed using the East 6 software package (Cytel Inc.).

Interim Analyses

There is no planned interim efficacy analysis for PFS.

Appendix 2
Schedule of Assessments

Assessment or Procedure	Screening Period	Treatment Period (Cycles 1 through Study Treatment Discontinuation)	Study Treatment Completion/Early Discontinuation [a]	Follow-Up *(± 14 Days)* [b]
	Days −28 to −1	Day 1 (±3 Days)		
Informed consent [c]	x			
Demographics [d]	x			
Medical history [e]	x			
Central HER2 and PDL-1 testing [f]	x			
Complete physical examination [g]	x			
Limited physical examination [h]		x	x	
ECOG performance status	x	x	x	
Weight [i]	x	x [h]		
Vital signs [j]	x	x [i]		
Hematology [k]	(7 days prior to C1D1)	x	x	
Serum chemistry [l]	(7 days prior to C1D1)	x [k]	x [k]	
Thyroid function test (TSH, free T3, and free T4)	x	C1D1 and every 4th cycle	x	
C-reactive protein	x			
INR and aPTT	x	As clinically indicated		
HIV, HCV, and HBV serology [m]	x			
Urinalysis [n]	x	As clinically indicated		
Pregnancy test [o]	x	x	*x*	x
Tumor and response assessment [p]	x	x		

Appendix 2
Schedule of Assessments (cont.)

Assessment or Procedure	Screening Period Days –28 to –1	Treatment Period (Cycles 1 through Study Treatment Discontinuation) Day 1 (±3 Days)	Study Treatment Completion/Early Discontinuation [a]	Follow-Up *(± 14 Days)* [b]
Bone scan/PET [q]	x	Perform as clinically indicated or as scheduled tumor assessment if only bone involvement at baseline		
CT or MRI of Brain [r]	Mandatory at screening	Perform as clinically indicated or as scheduled tumor assessment [r]		
12-Lead electrocardiogram [s]	x	Perform as clinically indicated		
NYHA classification	x			
ECHO or MUGA scan [t]	x	x Day 15–21 of Cycle 1, every fourth cycle thereafter. Additional LVEF measurements may be performed if LVEF declines are clinically suspected at the discretion of the investigator	x If not performed within 6 weeks of this visit	
Atezolizumab/placebo administration		x [w]		
Trastuzumab emtansine administration		x [x]		
PK/ATA		x (See Appendix 3)	x	
Blood Sample for Biomarker Analysis		x (See Appendix 4)	x	
Sample for auto-antibodies [u]	x			
Tissue Sample for Biomarker Analysis [v]		x (See Appendix 4)	x	
Concomitant medications	x	x	x	

Appendix 2
Schedule of Assessments (cont.)

Assessment or Procedure	Screening Period Days −28 to −1	Treatment Period (Cycles 1 through Study Treatment Discontinuation) Day 1 (±3 Days)	Study Treatment Completion/Early Discontinuation [a]	Follow-Up *(± 14 Days)* [b]
Adverse events	x	x	x	x
Survival follow-up				x [b]
Initiation of anti-cancer treatments				x [b]

CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBV = hepatitis B virus; HER2 = human epidermal growth factor receptor 2; IV = intravenous; LVEF = left ventricular ejection fraction; MBC = metastatic breast cancer; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Notes: With the exception of Day 1 of Cycle 1, all assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date.

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

[a] The treatment completion/discontinuation visit will optimally be scheduled for 28 − 42 days after the last dose of study treatment.

[b] Patients will be followed for survival, serious adverse events and adverse events of special interest considered as related to study drug (Section 5.3.1) and subsequent anti-cancer therapies (not all concomitant medications) need to be reported approximately every 3 months starting from the Study Drug Completion Visit until death, loss to follow-up, withdrawal of consent, or study discontinuation by the Sponsors. Survival follow-up information will be collected every 3 months via telephone calls, patient medical records, and/or clinic visits. Study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[c] Written informed consent must be obtained before any study-specific screening assessments are performed.

[d] Demographics include age, sex, and self-reported race/ethnicity.

Appendix 2
Schedule of Assessments (cont.)

[e] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the Cycle 1, Day 1 visit. Breast cancer history includes prior cancer therapies and procedures.

[f] Refer to Appendix 4 for tissue requirements related to eligibility. HER2 and or PDL-1 status may be determined outside of the screening window of 28 days.

[g] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] A limited physical examination consists of a symptom-driven physical examination that focuses on organ systems related to potential and ongoing adverse events and is based on the patient's clinical course during study treatment, the patient's medical history, and/or the known adverse event profiles of the study medications. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.

[j] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Hematology includes CBC, with RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Hematologic evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[l] Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[m] All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV DNA must be collected on or before Cycle 1, Day 1, in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

[n] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

Appendix 2
Schedule of Assessments (cont.)

[o] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test within 7 days prior to enrollment. During the treatment period, urine pregnancy test in women of childbearing potential in both treatment arms must be performed within 3 days prior study drug administration of every 3 cycles of protocol mandated therapy. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For patients who discontinue therapy before end of planned therapy, a pregnancy test must be done at the completion/early termination visit (approximately 28−42 days after the last dose of HER2-targeted therapy), and at 3 months and for HER2-targeted therapy, additionally at 6 months after the discontinuation of study treatment.

[p] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Radiologic imaging performed during the screening period should consist of 1) CT (with oral or IV contrast unless contraindicated) and/or MRI of the chest, abdomen, and pelvis, 2) bone scan or PET scan, 3) Brain MRI/CT and 4) any other imaging studies (CT of neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT of chest, abdomen, and pelvis performed during screening, then the patient should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study).

Tumor assessments will be performed at baseline, every 6 weeks ($\pm$7 days) following randomization, with additional scans as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of the following assessments every 6 weeks: 1) CT and/or MRI of the chest/abdomen/pelvis, as well as other known sites of disease*, including brain*, 2) If a patient has only bone as a site of involvement at screening which is determined to be measurable disease as per RECIST 1.1, then a bone scan or PET scan is mandated at each tumor assessment. Otherwise, a bone scan or PET scan is to be performed as clinically indicated, e.g., suspicion of disease progression, and 3) in cases where patients demonstrate control of their systemic disease but who newly develop isolated brain metastases and are eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments, *and* 4) any other imaging studies felt to be clinically indicated by the treating physician. Tumor response will be evaluated using RECIST v1.1 (Appendix 4 and immune-modified RECIST Appendix 5). In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first. Results must be reviewed by the investigator before dosing at the next cycle.

[q] An isotope bone scan and/or FDG PET will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

Appendix 2
Schedule of Assessments (cont.)

[r] CT/MRI scan of the brain *is mandatory at screening and should be performed 1) with scheduled tumor assesssments when identified as a site of involvement at baseline, 2) as clinically indicated, or 3) if a patient demonstrates control of systemic disease but has a newly developed isolated brain metastases and is eligible to remain on study treatment, a brain MRI or CT will be performed along with regularly scheduled tumor assessments.*

[s] A 12-lead ECG is required at screening. Subsequent ECGs may be performed as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[t] LVEF assessment by ECHO is preferred, but LVEF may also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

[u] Auto-antibody testing includes anti-nuclear antibody, anti–double-stranded DNA, and circulating and perinuclear cytoplasmic antibody. The baseline sample will be obtained pre-treatment Cycle 1, Day 1, before the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally.

[v] At screening, the FFPE archival tumor block from the most recently collected, available tumor tissue or fresh core biopsy (3 cores) is mandated. If more than 1 FFPE blocks exists from different time points e.g. initial diagnosis vs. metastatic disease tissue, the most recent block is mandatory to be sent. If the FFPE block from the earlier timepoint is available then this would be requested to also be sent. In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided. 20-25 freshly cut, unstained slides will be acceptable in lieu of the FFPE block. Optional core biopsies will be obtained at Cycle 1, Day 1 and Cycle 2, Day 1 (± 3 days) if patient consented. At the study drug discontinuation/early study completion visit, if reason for discontinuation is disease progression, a biopsy must be taken (if deemed clinically feasible) before next line of therapy begins, unless purely anti-hormonal therapy.

[w] Atezolizumab or placebo will be administered first by IV infusion at a dose of 1200 mg on Cycle 1, and on Day 1 of each 21-day cycle thereafter. For the first infusion of atezolizumab or placebo, vital signs should be determined within 60 minutes before, every 15 (± 5) minutes during, and 30 (± 10) minutes after the infusion, if clinically indicated. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms

[x] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Day 1 of Cycle 1, and on Day 1 of each 21-day cycle thereafter. For patients assigned to trastuzumab emtansine therapy, trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Samples

Table 1 Anti-Therapeutic Antibody and Pharmacokinetic Assessments for Atezolizumab[1]

Visit	Timepoint	Sample Type[a]
Cycle 1, Day 1 and Cycle 4 Day 1	Pre-infusion[b] of atezolizumab or placebo	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab
Cycle 1, Day 1 and Cycle 4 Day 1	30 minutes (±10 mins) after end of atezolizumab or placebo infusion	Serum sample for atezolizumab pharmacokinetics
Cycles 2, 3, 8, and every 8 cycles thereafter, Day 1 (±3 days)	Pre-infusion [b] of atezolizumab or placebo	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab
Study treatment/early discontinuation visit	At any time during visit	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab
120 days (±28 days) after treatment completion or discontinuation	At any time during visit	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab

ATA = anti-therapeutic antibody.

[a] Blood for PK/ ATA should not be obtained through the same line that atezolizumab or placebo is infused.

[b] Within 24 hours prior to atezolizumab infusion.

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

Table 2 Anti-Therapeutic Antibody and Pharmacokinetic Assessments for Trastuzumab Emtansine[1]

Visit	Timepoint	Sample Type[a]
Cycle 1, Day 1 and Cycle 4 Day 1	Pre-infusion[b] of trastuzumab emtansine	Serum sample for trastuzumab emtansine and total trastuzumab pharmacokinetics Serum HER2 ECD (Cycle 1 only) Plasma sample for DM1 (Cycle 1 only) Serum sample for ATA to trastuzumab emtansine
Cycle 1, Day 1 and Cycle 4 Day 1	30 minutes (±10 mins) after end of trastuzumab emtansine infusion	Serum sample for trastuzumab emtansine and total trastuzumab Plasma sample for DM1
Cycle 2, Day 1 (±3 days)	Pre-infusion [b] of trastuzumab emtansine	Serum sample for trastuzumab emtansine and total trastuzumab
Study treatment/early discontinuation visit	At any time during visit	Serum sample for trastuzumab emtansine pharmacokinetics
		Serum sample for ATA to trastuzumab emtansine
120 days (±28 days) after treatment completion or discontinuation	At any time during the visit	Serum sample for ATA to trastuzumab emtansine

ATA = anti-therapeutic antibody.

[a] Blood for PK/ ATA should not be obtained through the same line that trastuzumab emtansine is infused.

[b] Within 24 hours prior to Trastuzumab emtansine administration.

Appendix 4
Schedule of Biomarker Samples

Table 3 Blood Samples for Biomarker Analysis

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pre-infusion	Whole blood sample [a]
		Whole blood RBR sample for genetic research
		Blood for serum/plasma
Cycle 2, Day 1	Pre-infusion	Whole blood sample [a]
		Blood for serum/plasma
Cycle 3, Day 1	Pre-infusion	Blood for serum/plasma
Cycle 8, Day 1	Pre-infusion	Blood for serum/plasma
Study treatment/early discontinuation visit	At any time during visit	Whole blood sample [a]
		Blood for serum/plasma
120 days (± 28 days) after treatment completion or discontinuation	At any time during visit	Whole blood sample [a]
		Blood for serum/plasma

[a] Whole blood sample will be taken from all patients enrolled on the study. Serial sample collection will be collected on approximately the first 50 enrolled patients only.

Table 4 Tissue Sample for Biomarker Analysis

Visit	Timepoint	Requirement	Sample Type
Screening	Pre-infusion	Mandatory	FFPE archival tumor block or partial block most recently collected, available tumor tissue or Fresh core biopsy (3 cores) If more than 1 FFPE blocks exists from different time points e.g. initial diagnosis vs. metastatic disease tissue, the most recent block or partial block is mandatory to be sent. If the FFPE block from the earlier timepoint is available then this would be requested to also be sent. In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided Upon discussion with the Medical Monitor (in case of site regulations that prevent sending a block), 20 freshly cut, unstained slides will be acceptable in lieu of FFPE block. If only fewer than 20 unstained slides are available at baseline (but no fewer than 15), discuss with the Medical Monitor to decide on eligibility.
Cycle 1 Day 1	Pre-infusion (within 28 days of C1D1)	Optional	Fresh Core Biopsy (3 cores) FFPE block or partial block preferred or freshly cut, unstained 15 slides
Cycle 2 Day 1	Pre-infusion (within 3 days prior to C2D1 or up to 5 days after C2D1)	Optional	Fresh Core Biopsy (3 cores) FFPE block or partial block preferred or freshly cut, unstained 15 slides
Study treatment/early discontinuation visit Reason: Disease Progression	At time of Study treatment/early discontinuation visit (if the reason for discontinuation was PD) Must be taken before next line of therapy begins. In case new line therapy is purely anti-hormonal, biopsy could be taken after it is started.	Mandatory (if deemed clinically feasible)	Fresh Core Biopsy (3 cores) at site of progression if accessible or from any other lesion FFPE block preferred or freshly cut, unstained 15 slides