Official Title: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase III Study of the Efficacy and Safety of Trastuzumab Emtansine in Combination with Atezolizumab or Placebo in Patients with HER2-Positive and PD-L1-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab- (+/- Pertuzumab) and Taxane-Based Therapy (KATE3)

NCT Number: NCT04740918

Document Date: SAP Version 1: 28-March-2023

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR PLACEBO IN PATIENTS WITH HER2-POSITIVE AND PD-L1−POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB (±PERTUZUMAB) AND TAXANE-BASED THERAPY**
STUDY NUMBER:	MO42319
STUDY NAME:	KATE3
VERSION NUMBER:	1
ROCHE COMPOUND(S):	Trastuzumab Emtansine (RO5304020) Atezolizumab (RO5541267)
EUDRACT NUMBER:	2020-002818-41
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PLAN PREPARED BY:	[redacted] (Cytel) and [redacted] (Roche)

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR: **LEGAL REGISTERED ADDRESS:**	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document.

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document dated 28 February 2022.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic date stamp on the final page of this document.	Version 4, 2 March 2023

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
AESI	Adverse event of special interest
CI	confidence interval
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
eCRF	electronic Case Report Form
HER2	Human Epidermal Growth Factor Receptor
HR	hazard ratio
iDCC	Independent Data Coordinating Center
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
Inv-PFS	Investigator-based PFS
IRB	Institutional Review Board
IRF	Independent Review Facility
ITT	intent to treat
IxRS	interactive voice/web response system
LABC	locally advanced breast cancer
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPT	non-protocol anti-cancer therapy
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PgR	progesterone receptor

Abbreviation or Term	Description
PR	partial response
q3w	every 3 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
SAP	Statistical Analysis Plan
T-DM1	Trastuzumab Emtansine
TIL	tumor-infiltrating lymphocyte
ULN	upper limit normal
US	United States of America

1. INTRODUCTION

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol MO42319 for the purposes of a regulatory filing.

This SAP details the planned analyses and statistical methods for Study MO42319 (KATE3), "A Phase III, Randomized, Multicenter, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Trastuzumab Emtansine in Combination with Atezolizumab or Placebo in patients with HER2-Positive and PD-L1-Positive Locally Advanced or Metastatic Breast Cancer who have received Prior Trastuzumab (±Pertuzumab) and Taxane-Based Therapy". For background information about the study, refer to Protocol MO42319.

Of note, the Sponsor has decided to prematurely terminate the study due to a lower-than-expected enrolment rate, which significantly extended the recruitment timelines. For more details, refer to Protocol MO42319.

There are no changes to the planned analyses described in the Protocol MO42319 version 4.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics and patient-reported outcomes of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo in patients with human epidermal growth factor 2 (HER2)-positive and programmed death-ligand 1 (PD-L1)-positive locally advanced (LABC) or metastatic breast cancer (MBC). Patients must have progressed either during or after prior trastuzumab- (±pertuzumab) and taxane-based therapy for LABC or MBC; or during (or within 6 months after completing) trastuzumab- (±pertuzumab) and taxane-based therapy in the neoadjuvant and/or adjuvant setting.

In this SAP, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., trastuzumab emtansine and atezolizumab or trastuzumab emtansine and placebo).

Following the Sponsor's decision to prematurely terminate the study, as outlined in protocol, specific study objectives are no longer applicable and corresponding analyses will not be conducted. Specific objectives and corresponding endpoints for the study which are still applicable after the Sponsor's decision to prematurely terminate the study are outlined in Table 1.

Study objectives and endpoints will be further described using the estimand framework, in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To demonstrate superiority of the experimental over the control treatment in either or both comparisons	• PFS, defined as the time from randomization to the first occurrence of any of the events defined below (whichever occurs first): – Disease progression, as determined by investigator assessment using RECIST v1.1 – Death from any cause • OS, defined as the time from randomization to death from any cause
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo	• ORR, defined as CR or PR on two consecutive assessments at least 28 days apart, as determined by investigator assessment using RECIST v1.1 • DOR, 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 • PFS in patients with baseline brain metastases as determined by investigator assessment using RECIST version 1.1 • OS in patients with baseline brain metastases defined as the time from randomization to death from any cause • CNS PFS as determined by investigator assessment using RECIST v1.1 in patients with or without baseline CNS metastases
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo	• Incidence and severity of AEs, with severity determined according to NCI CTCAE v5.0 • Change from baseline in targeted clinical laboratory test results

Table 1 Objectives and Corresponding Endpoints (Cont.)

Exploratory Biomarker Objective	Corresponding Endpoints
• To identify and/or evaluate biomarkers that are predictive of response to atezolizumab in combination with trastuzumab emtansine (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 and trastuzumab emtansine, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of atezolizumab and/or trastuzumab emtansine activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Association of baseline stromal TILs with efficacy • Association of baseline HER2 expression level (protein and/or gene amplification status) with efficacy • Association of baseline PD-L1 expression level ($\geq$1% and $<$5% IC vs $\geq$5% IC) with efficacy • Description of prevalence and correlation among biomarkers in tumor tissue

AE = adverse event; CNS = central nervous system; CR = complete response; DOR = duration of response; HER2 = Human Epidermal growth factor Receptor; IC = tumor-infiltrating immune cell; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression free survival; PR = partial response; RECIST = response evaluation criteria in solid tumors; TIL = tumor-infiltrating lymphocytes.

1.2 STUDY DESIGN

This is a Phase III, randomized, multicenter, international, two-arm, double-blind, placebo-controlled study. Patients will be randomized to one of the following treatment arms in a 1:1 ratio:

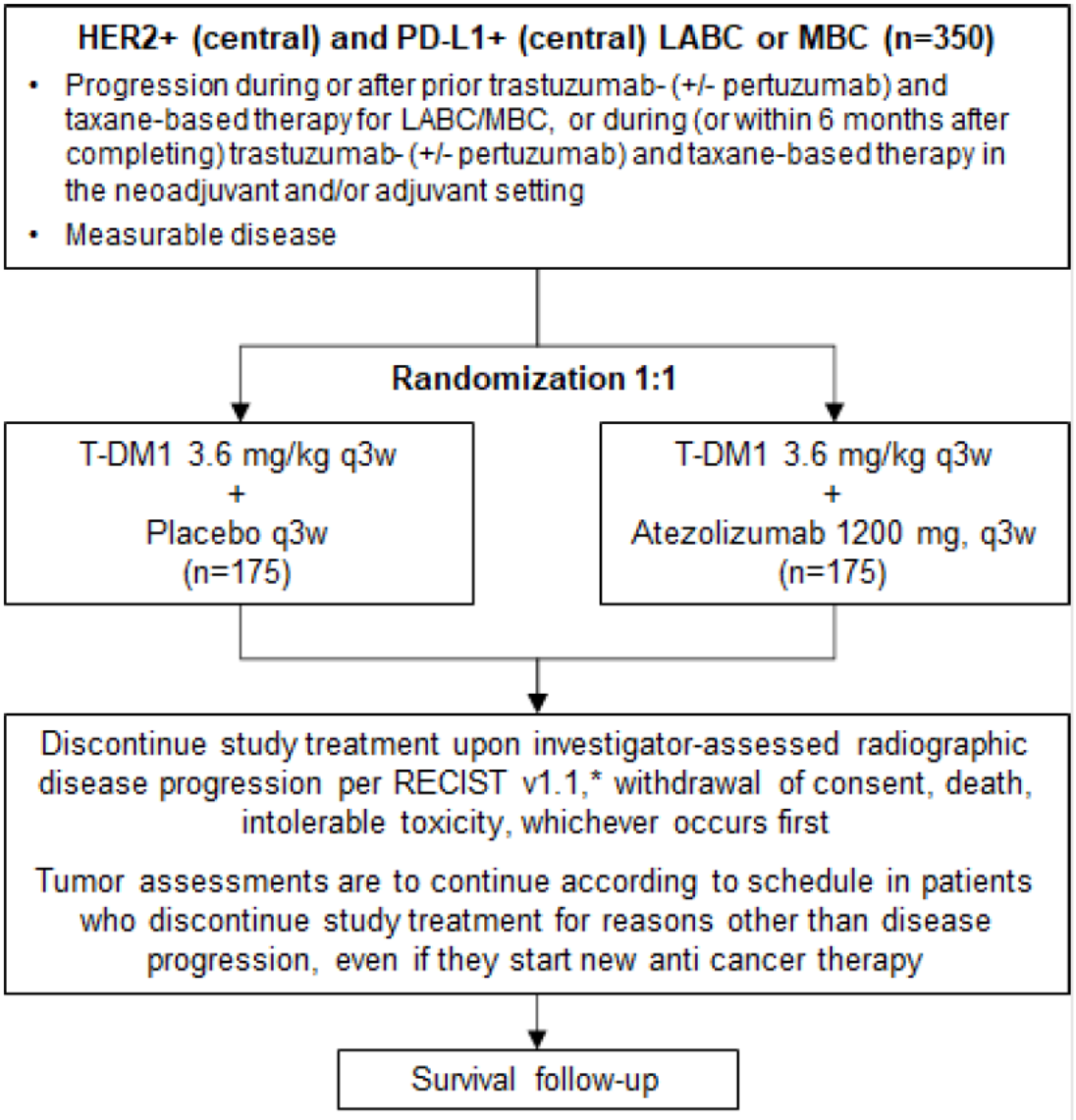
- Arm A: trastuzumab emtansine 3.6mg/kg and placebo, every 3 weeks (q3w)
- Arm B: trastuzumab emtansine 3.6mg/kg and atezolizumab 1200 mg, q3w

This study initially planned to enroll approximately 350 patients in approximately 175 sites worldwide.

Following the Sponsor's decision to prematurely terminate the study, the initially planned number of randomized patients will not be reached.

The study schema is shown in Figure 1.

Figure 1 Study Schema



HER2 = human epidermal growth factor receptor; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; PD-L1 = programmed cell death protein 1; q3w = every 3 weeks; RECIST = response evaluation criteria in solid tumors; T-DM1 = trastuzumab emtansine.

Notes: Stratification factors: Local hormonal status (ER and/or PgR positive vs. ER and PgR negative/unknown); Disease status (visceral metastasis without brain metastasis vs. non-visceral metastasis only without brain metastasis [including locally advanced disease] vs. brain metastasis); World Region (Western Europe vs. U.S. vs; Rest of World).

*Patients with isolated CNS progression that require local therapy only will be allowed to continue with study treatment as per investigator decision. These patients will be recorded as disease progression for PFS analysis but will remain blinded and continue with treatment as per initial randomization.

1.2.1 Treatment Assignment and Blinding

This is a randomized, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and

eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Patient will be randomly assigned to one of two treatment arms: trastuzumab emtansine plus atezolizumab or trastuzumab emtansine plus placebo. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Arm A and Arm B will be blinded with respect to administration of atezolizumab or placebo. Crossover between treatment arms will not be permitted.

Randomization will be stratified according to the following criteria:

- Local hormonal status (estrogen receptor [ER] and/or progesterone receptor [PgR] positive vs. ER and PgR negative/unknown),
- Disease status (visceral metastasis without brain metastasis vs. non-visceral metastasis only without brain metastasis [including locally advanced disease] vs. brain metastasis),
- World Region (Western Europe vs. U.S. vs. Rest of World).

The Sponsor has decided to prematurely terminate the study due to a lower-than-expected enrolment rate, which significantly extended the recruitment timelines. The investigators were informed of premature study termination on 15 December 2022 by a study memo communicating this decision.

Following a discussion between the investigator and the patient regarding the premature termination, the patient may consent to continue study treatment (i.e., either trastuzumab emtansine and atezolizumab or trastuzumab emtansine as a single agent; placebo will no longer be administered following unblinding of treatment assignment) if considered clinically appropriate by the investigator.

The Sponsor's rationale for unblinding the study is to allow investigators and patients to have an open discussion of the potential benefits and risks of continuing the experimental therapy and to allow them to continue with treatment options off this study. The Sponsor's decision to unblind the study with respect to treatment assignment, was made after consideration of the following factors.

The analysis of the two primary efficacy endpoints of progression-free survival (PFS) based on investigator tumor assessment and overall survival (OS) will no longer be conducted under an alpha-controlled framework as per the original study design. The analyses of PFS and OS will be reported in a descriptive way with no formal statistical testing performed and no control for the overall type I error (α) accounting for the two primary endpoints. Consequently, the p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

Unblinding will be required for patients to continue with off-study treatment options.

After unblinding of patients' treatment assignment, patients will continue to receive study treatments until off-study treatment options are put into place. More details are provided in the study protocol.

1.2.2 Independent Review Facility

An independent review facility will be used for this study to collect and retain copies of tumor assessment scans for centralized review. The independent reading will be blinded to the treatment information as well as subject demographics and tumor assessments from the site (more details described in the imaging charter).

Following premature study termination, tumor assessment scans will no longer be collected prospectively by the Sponsor and an IRF will not be utilized.

1.2.3 Data Monitoring

An independent data monitoring committee (iDMC) will evaluate safety and efficacy data during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis, approximately every 6 months from the time of the enrollment of the first patient. All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC).

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

As per the iDMC charter, the iDMC will perform review of unblinded safety data until the study is unblinded, after which the study team will be responsible for the ongoing monitoring of patient safety in the study. Accordingly, the iDMC review activities will stop once the unblinding of the study will have been performed following the Sponsor's decision for premature study termination.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

Following the Sponsor's decision to prematurely terminate the study, the analysis of the two primary efficacy endpoints of PFS based on investigator tumor assessment and OS will no longer be conducted under an alpha-controlled framework as per the original study design. The analyses of PFS and OS will be reported in a descriptive way with no formal statistical testing performed and no control for the overall type I error (α)

accounting for the two primary endpoints. Consequently, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

2.2 SAMPLE SIZE DETERMINATION

The two primary efficacy endpoints for this study are PFS based on investigator tumor assessment and OS.

This study has been designed to detect a substantial magnitude of benefit in the intent to treat (ITT) population, that is, improvement in median PFS from 7 months in the control arm to 11.67 months in the experimental arm, corresponding to a target PFS hazard ratio of 0.60, and improvement in median OS from 31 months in the control arm to 47.7 months in the experimental arm, corresponding to a target OS hazard ratio of 0.65.

Initially, it was planned that approximately 350 patients randomized according to a 1:1 randomization (approximately 175 patients will be randomized to Arm A and to Arm B) would be enrolled in the study. The sample size assumed an annual dropout rate of 10% in both treatment arm and resulted in an estimated recruitment time of about 32 months (with ramp up in the first 8 months). Following the Sponsor's decision to prematurely terminate the study, the initially planned number of randomized patients will not be reached.

Furthermore, in the context of premature study termination, there will be only a single analysis timepoint for both PFS and OS primary efficacy endpoints. Interim analyses will no longer be conducted. Considering the expected lack of maturity of the data, the analysis of PFS and OS primary efficacy endpoints will no longer be conducted under an alpha-controlled framework as per the original study design. The analyses of PFS and OS will be reported in a descriptive way with no formal testing performed and no control for the overall type I error (α) accounting for the two primary endpoints. Consequently, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

3. ANALYSIS SETS

The analysis sets for this study are defined in Table 2 below.

Table 2 Analysis Sets

Population	Definition
Intention-to-treat (ITT)	All randomized participants, whether or not they received any study medication. Patients will be grouped according to the treatment assigned at randomization by the IxRS.
Safety-evaluable	All participants randomly assigned to study treatment and who received at least one full or partial dose of study drug. Patients will be analyzed based on the treatment they actually received (which may be different from the treatment the patient was randomized to).

Population	Definition
Subset ITT with brain metastases at baseline	All participants included in the ITT with brain metastasis at randomization as collected by the IxRS
Subset ITT with CNS metastases at baseline	All participants included in the ITT with CNS metastasis at baseline as collected by eCRF
Subset ITT without CNS metastases at baseline	All participants included in the ITT without CNS metastasis at baseline as collected by eCRF
Subset ITT with measurable disease	All participants included in the ITT with a measurable disease at baseline.
Screen Failed population with PD-L1 negative status	All screen failed patients with a PD-L1 negative status

CNS = Central Nervous System; ITT = intent-to-treat; IxRS = interactive voice/web response system

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

All efficacy analyses will be performed on the ITT population, unless otherwise specified. Participants will be analyzed according to the treatment assigned at randomization by the IxRS.

All safety analyses will be performed in the safety-evaluable population, unless otherwise specified. Participants will be analyzed according to the treatment they actually received.

Analyses of demographics and other baseline information will be based on the ITT population, and per treatment assigned by the IxRS, unless otherwise specified.

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

In safety analyses, all deaths are included, from all sources, regardless of completeness of death date; participants who died with only a partial death date available will be included. In efficacy analyses, a death is considered an event if and only if a complete death date is available; participants who died with only a partial death date available will be censored on their last date known to be alive plus 1 day.

4.2 PARTICIPANT DISPOSITION

Patient enrollment will be tabulated by study site for each treatment arm. Duration of follow-up, discontinuation from study treatment and study, and reasons for discontinuation, will be summarized by treatment arm to which patients were randomized. In addition, major protocol violations will be summarized by treatment arm.

4.3 PRIMARY ENDPOINTS ANALYSIS

4.3.1 Definition of Primary Endpoint(s)/Estimand(s)

The multiple primary efficacy endpoints for this study are PFS based on investigator tumor assessment and OS.

Investigator-based PFS (Inv-PFS) is defined as the time from randomization to the date of first occurrence of any of the events defined below (whichever occurs first):

- First documented disease progression as determined by the investigator using RECIST 1.1
- Death from any cause

The first documented disease progression will be used in the analysis of the primary efficacy endpoint of PFS.

Data for patients without an event 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. Data from patients who have had two or more missing or unevaluable tumor assessments prior to a PFS event will be censored in the same approach. These scenarios are considered non-informative missing data.

The primary estimand for Inv-PFS is defined as follows:

- Population: Patients with HER2-positive and PD-L1-positive locally advanced or metastatic breast cancer who have received prior trastuzumab (±pertuzumab) and taxane-based therapy, as defined by the inclusion and exclusion criteria in Protocol MO42319
- Variables: Time from randomization to the first occurrence of a PFS event, as defined above
- Treatments:
  - Experimental: trastuzumab emtansine 3.6 mg/kg by IV infusion q3w plus atezolizumab 1200 mg by IV infusion q3w
  - Control: trastuzumab emtansine 3.6 mg/kg by IV infusion q3w plus placebo by IV infusion q3w
- Intercurrent events:
  - Start of non-protocol anti-cancer therapy (NPT) prior to a PFS event
  - Early discontinuation from study treatment for any reason prior to a PFS event
- Handling of intercurrent events:

  - A treatment policy with regards to the listed intercurrent events will be applied for the main analysis (i.e., taking the date of the recorded PFS event ignoring the occurrence of those intercurrent events)
- Summary measure: Hazard ratio for PFS

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 one day.

The primary estimand for OS is defined as follows:

- Population: Patients with HER2-positive and PD-L1-positive locally advanced or metastatic breast cancer who have received prior trastuzumab (±pertuzumab) and taxane-based therapy, as defined by the inclusion and exclusion criteria in Protocol MO42319
- Variables: Time from randomization to death from any cause
- Treatments:
  - Experimental: trastuzumab emtansine 3.6mg/kg by IV infusion q3w plus atezolizumab 1200 mg by IV infusion q3w
  - Control: trastuzumab emtansine 3.6mg/kg by IV infusion q3w plus placebo by IV infusion q3w
- Intercurrent events:
  - Start of NPT
  - Early discontinuation from study treatment for any reason
- Handling of intercurrent events:
  - A treatment policy with regards to the listed intercurrent events will be applied for the main analysis (i.e., taking the date of the recorded OS event ignoring the occurrence of those intercurrent events)
- Summary measure: Hazard ratio for OS

4.3.2 Main Analytical Approach for Primary Endpoint(s)

Progression-Free Survival

The Kaplan-Meier method will be used to estimate median PFS and the corresponding 95% CIs for each treatment arm. The two-sided log-rank test, stratified by the factors specified in the protocol (excluding world region) will be used to compare PFS between the treatment arms. If less than five events are observed in any combination of stratification factors, only the unstratified analysis will be done. The stratification factors will be based on data collected by the IxRS rather than on data collected on the eCRFs.

The Cox proportional hazards model, stratified by the previous noted stratification factors, excluding world region, will be used to estimate the hazard ratio (HR) and to calculate the 95% confidence interval (CI) of the HR.

Overall Survival
Methods for data analysis are analogous to those described for the primary efficacy endpoint PFS.

4.3.3 Sensitivity Analyses

No sensitivity analyses are planned for the primary endpoints.

4.3.4 Supplementary Analyses

No supplementary analyses are planned for the primary endpoints.

4.3.5 Subgroup Analyses for Primary Endpoint(s)

Subgroup analyses related to stratification factors will be conducted based on stratification factors as reported in the IxRS system and repeated based on stratification factors as reported on the eCRF.

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

- Age category ($<$65 vs 65-74 vs. $\geq$75 years)
- Race (Caucasian, black, Asian, and other)
- World region (US, Western-Europe, Asia, Other)
- Eastern Cooperative Oncology Group (ECOG) status (0, 1, or unknown)
- Hormone receptor status (ER/PgR negative vs ER and/or PgR positive vs unknown)
- Disease involvement (visceral disease vs non-visceral disease)
- Brain metastasis (Y/N)
- Liver metastasis (Y/N)
- Number of lines of prior therapy for metastatic disease (0, 1 or $\geq$2)
- Prior pertuzumab for metastatic (Y/N)
- Prior trastuzumab deruxtecan for metastatic (Y/N)
- Prior PD-1/PD-L1 therapy (Y/N)
- Status of disease (metastatic, locally advanced)
- Prior neoadjuvant therapy (pertuzumab, other, or no prior neoadjuvant therapy)
- Prior adjuvant therapy (trastuzumab emtansine, pertuzumab, other, or no prior adjuvant therapy)

4.4 SECONDARY ENDPOINTS ANALYSES

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

4.4.1 Objective Response Rate

Objective response, defined as a complete response (CR) or partial response (PR), will be determined by investigator tumor assessment using RECIST v1.1. 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. For patients who received a NPT, only tumor assessments prior to the start of non-protocol anti-cancer therapy will be considered in the derivation of ORR.

Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Wilson score confidence interval) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified by local hormonal status and disease status will be used to compare response rates between treatment arms.

The estimand for ORR will be as follows:

- Population: As defined for the primary endpoint in Section 4.3.1 and with measurable disease at baseline
- Variable: Objective response, defined as a confirmed CR or PR, as determined by investigator tumor assessment using RECIST v1.1
- Treatments: As defined for the primary endpoint in Section 4.3.1
- Intercurrent events:
  - Start of NPT prior to response
  - Early discontinuation from study treatment for any reason prior to response
- Handling of intercurrent events:
  - While not having started NPT (i.e., only tumor assessments prior to the start of non-protocol anti-cancer therapy are included for derivation of ORR)
  - Treatment policy for early treatment discontinuation (i.e., this intercurrent event is ignored for derivation of ORR).
- Summary measure: Odds ratio for ORR

An unstratified Chi-squared test will also be provided as sensitivity analysis. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

Descriptive analysis on the same subgroup analyses for primary endpoints will also be performed for ORR.

4.4.2 Duration of Response

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. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a response, duration of response will be censored at the date of the first occurrence of a response. Patients who received a NPT before their documented disease progression or death will be censored at the last tumor assessment date prior to the start date of this non-protocol anti-cancer therapy.

The estimand for the key secondary endpoint is defined as follows:

- Population: As defined for the primary endpoint in Section 4.3.1 and also experienced an objective response
- Treatments: As defined for the primary endpoint Section 4.3.1
- Variable: Time interval from the date of the first occurrence of an objective response (PR or CR) determined by investigator tumor assessment using RECIST v1.1 until the first date that progressive disease or death for any cause, whichever occurs first
- Intercurrent events:
  - Early discontinuation from treatment for any reason while responding
  - Start of NPT while responding
- Handling of intercurrent events:
  - In case of early discontinuation from treatment for any reason, a treatment policy will be applied (i.e., taking the date of the recorded event ignoring the occurrence of this intercurrent event)
  - In case of start of NPT while responding, an hypothetical strategy will be applied (i.e., censoring patient at the last tumor assessment date prior to the start date of this non-protocol anti-cancer therapy)
- Summary measure: Hazard ratio for duration of response (DOR)

The analysis methods are similar to those described for the primary efficacy endpoints PFS and OS in Section 4.3.2.

4.4.3 Progression-Free Survival in Patients with Baseline Brain Metastases

PFS, 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 first, in patients with baseline brain metastases.

The estimand for the secondary endpoint is defined as follows:

- Population: Subset of ITT with brain metastasis at baseline
- Treatments: As defined for the primary endpoint in Section 4.3.1
- Variable: Time from randomization to the first occurrence of a PFS event
- Intercurrent events:
  - Start of NPT prior to a PFS event
  - Early discontinuation from study treatment for any reason prior to a PFS event
- Handling of intercurrent events: A treatment policy with regards to the listed intercurrent events will be applied for the secondary analysis (i.e., taking the date of the record PFS event ignoring the occurrence of those intercurrent events)
- Summary measure: Hazard ratio for PFS

The analysis methods are similar to those described for the primary efficacy endpoints PFS and OS in Section 4.3.2.

4.4.4 Overall Survival in Patients with Baseline Brain Metastases

Overall survival, defined as the time from randomization to the date of death from any cause, in patients with baseline brain metastases.

The estimand for the secondary endpoint is defined as follows:

- Population: Subset of ITT with brain metastasis at baseline
- Treatments: As defined for the primary endpoint in Section 4.3.1
- Variable: Time from randomization to death from any cause
- Intercurrent events:
  - Start of NPT
  - Early discontinuation from study treatment for any reason
- Handling of intercurrent events: A treatment policy with regards to the listed intercurrent events will be applied for the secondary analysis (i.e., taking the date of the recorded OS event ignoring the occurrence of those intercurrent events)
- Summary measure: Hazard ratio for OS

The analysis methods are similar to those described for the primary efficacy endpoints PFS and OS in Section 4.3.2.

4.4.5 Central Nervous System Progression-Free Survival

Central nervous system (CNS) PFS is defined as the time from randomization until CNS disease progression, or first occurrence of symptomatic CNS disease, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first, in the subgroups of patients with or without CNS metastases at baseline.

Patients who have experienced non-CNS progression at the time of analysis will be censored at the date of this progression. Patients who have experienced no disease progression and are alive at the time of analysis will be censored at the date of their last post-baseline tumor assessment or, if they have no post-baseline tumor assessment, on the date of randomization + 1 day.

The estimand for the secondary endpoint is defined for population 1 and 2 separately as follows:

- Population 1: Subset of ITT with CNS metastases at baseline
- Population 2: Subset of ITT without CNS metastases at baseline
- Treatments: As defined for the primary endpoint in Section 4.3.1
- Variable:
  - Time from randomization until CNS disease progression, or first occurrence of symptomatic CNS disease or death from any cause, as defined above
- Intercurrent events:
  - Start of NPT prior to a CNS-PFS event
  - Early discontinuation from study treatment for any reason prior to a CNS-PFS event
- Handling of intercurrent events: A treatment policy with regards to the listed intercurrent events will be applied for the secondary analysis (i.e., taking the date of the recorded CNS-PFS event ignoring the occurrence of those intercurrent events)
- Summary measure: Hazard ratio for CNS-PFS

The analysis methods are similar to those described for the primary efficacy endpoints PFS and OS in Section 4.3.2.

In addition, in order to account for the competing risks inherent in the comparison of CNS progression between treatments, a stratified two-sided log-rank test will be computed on the basis of a cause-specific hazard function. Results from unstratified tests will also be presented as supportive analyses.

The probability of CNS progression, non-CNS progression, and death by treatment group with 95% CIs will each be estimated using cumulative incidence functions. Gray's test to compare the risk of CNS progression between treatments will also be presented.

4.5 SAFETY ANALYSES

Patients who receive any amount of study treatment will be included in the safety analyses. Safety results will be summarized based on the treatment patients actually received. Specifically, a patient will be included in the trastuzumab emtansine plus atezolizumab arm in safety analyses if the patient received any amount of atezolizumab.

Safety will be assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs and ECGs.

4.5.1 Extent of Exposure

Study treatment exposure, such as treatment duration, total dose received, number of cycles, and dose modification (including dose delay, dose reduction, etc.) will be summarized for each study treatment on each treatment arm with descriptive statistics. Reasons for study treatment discontinuation will also be summarized.

4.5.2 Adverse Events

Verbatim descriptions of 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) v5.0. The following events occurring on or after the first dose of study treatment (i.e., treatment-emergent AEs) will be summarized by NCI CTCAE v5.0 grade:

- All AEs
- Serious adverse events
- AEs leading to death
- AEs of special interest (AESI)
- AEs leading to study drug discontinuation
- AEs leading to dose reduction (T-DM1)
- AEs leading to drug interruption
- AEs reported as COVID-19
- Selected AEs

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

Deaths and cause of death will be summarized.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

Relevant laboratory values and change from baseline will be summarized by treatment arm over time, with NCI CTAE v5.0 Grade 3 and Grade 4 value identified, where appropriate.

Summary tables of shifts in NCI CTCAE v5.0 grades from baseline to the worst post-baseline value will be presented.

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

In order to describe the AESI as well, the number of patients with ALT or AST $>10\times$ULN will be provided.

4.5.3.2 Vital Signs

Vital signs parameters (pulse rate, respiratory rate, blood pressure and temperature) will be summarized descriptively over time including change from baseline.

4.5.3.3 ECGs

Electrocardiogram (ECG) data will be summarized over time including change from baseline.

4.5.3.4 Left Ventricular Ejection Fraction

Change in left ventricular ejection fraction (LVEF) from baseline over time will be summarized for each treatment arm.

The number of patients with a drop in LVEF of ≥ 10 ejection fraction points from baseline to an LVEF of $<50\%$ will be summarized. The maximum decrease in LVEF from baseline will be summarized by treatment arm. In addition, the lowest available LVEF 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.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Patient disposition will be summarized as outlined in Section 4.2.

Duration of follow-up will be summarized by treatment arm to which patients were randomized.

In addition, major protocol deviations, including major deviations with regards to the inclusion and exclusion criteria, and major deviations resulting from the COVID-19 pandemic, will be summarized by treatment arm.

4.6.2 Summaries of Treatment Group Comparability

The evaluation of treatment group comparability between the two treatment arms will include summaries of demographics, breast cancer history, baseline characteristics, patient treatment history, prior cancer therapy and a summary of randomization stratification factors.

Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables such as age or time since initial breast cancer diagnosis. Frequency counts will be presented by treatment arm for categorical variables such as gender, race, and age category (<65, $65–74$, ≥ 75).

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

4.6.3 Biomarker Analyses

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

Exploratory biomarkers analyses will be conducted to assess the relationship between biomarkers in tumor tissue as appropriate.

Descriptive analysis of PFS and OS will be conducted within following biomarker subgroups:

- Stroma tumor-infiltrating lymphocytes (TIL)
  - $<$median vs. $\geq$median
  - $<$5% vs. $\geq$5%
  - low (0-10%) vs intermediate (11-60%) vs high ($>$60%)
- Intratumoral TILs ($<$1% vs. $\geq$1%)
- PD-L1 status ($\geq$1% and $<$5% IC vs $\geq$5% IC and tumor cell %)
- HER2 immunohistochemistry (IHC) status IHC0 vs IHC1+ vs IHC2+ vs IHC3+
- HER2 IHC focal ($<$30% tumor cells) vs heterogeneous (30–79% tumor cells) vs homogeneous ($>$80% tumor cells)
- Patients with HER2 in situ hybridization amplified vs non-amplified

4.6.4 Screen Failure Analysis

The Screen Failure Analysis is an exploratory analysis, which will consist into comparisons of the screen failed patients with a PD-L1 negative status versus the patient included in the ITT population. Note that all patients included in the ITT population should have a PD-L1 positive status as per the inclusion criteria. The comparisons will include demographics, breast cancer history, prior cancer therapy and tissue sample collection data. Further data may be included as deemed appropriate. The data will be summarized by patient group (ITT population and Screen Failures with negative PD-L1 Status) and overall.

4.7 INTERIM ANALYSES

4.7.1 Planned Interim Analyses

Following the Sponsor's decision to prematurely terminate the study, interim analyses will no longer be conducted.

4.7.2 Optional Interim Analyses

No optional interim analyses are planned for this study.

5. SUPPORTING DOCUMENTATION

This section is not applicable since there is no additional supporting document.

6. REFERENCES

References are available on request.

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR PLACEBO IN PATIENTS WITH HER2-POSITIVE AND PD-L1-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB- (+/- PERTUZUMAB) AND TAXANE-BASED THERAPY (KATE3)**
PROTOCOL NUMBER:	MO42319
VERSION NUMBER:	4
EUDRACT NUMBER:	2020-002818-41
IND NUMBER:	71,072
NCT NUMBER:	NCT04740918
TEST PRODUCT:	Trastuzumab Emtansine (RO5304020) Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Locally advanced / metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and patient-reported outcomes of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo in patients with human epidermal growth factor 2 (HER2)-positive and programmed death-ligand 1 (PD-L1)-positive locally advanced (LABC) or metastatic breast cancer (MBC). Patients must have progressed either during or after prior trastuzumab- (±pertuzumab) and taxane-based therapy for LABC/MBC; or during (or within 6 months after completing) trastuzumab- (±pertuzumab) and taxane-based therapy in the neoadjuvant and/or adjuvant setting.

Specific objectives and corresponding endpoints for the study are outlined below.

PRIMARY EFFICACY OBJECTIVE

The trial will compare trastuzumab emtansine given at a dose of 3.6 mg/kg by IV infusion, q3w plus atezolizumab administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle with trastuzumab emtansine given at a dose of 3.6 mg/kg by IV infusion, q3w plus placebo administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle in patients with HER2-positive and PD-L1-positive LABC or MBC who have progressed either during or after prior trastuzumab- (±pertuzumab) and taxane-based therapy for LABC/MBC, or during (or within 6 months after completing) trastuzumab- (±pertuzumab) and taxane-based therapy in the neoadjuvant and/or adjuvant setting.

The two primary comparisons of interest will be the hazard ratios for PFS and OS as defined below. The primary trial objective is to demonstrate superiority of the experimental over the control treatment in either or both comparisons.

- Progression-free survival (PFS), defined as the time from randomization to the first occurrence of documented disease progression, as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from randomization to death from any cause

Following the Sponsor's decision to prematurely terminate the study, these objectives are no longer applicable. Accordingly, the analyses of PFS and OS will only be reported in a descriptive way. No formal testing will be performed and no control for the overall type I error (α) accounting for the two primary endpoints will be implemented. Consequently, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

SECONDARY EFFICACY OBJECTIVE

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

- Objective response rate (ORR), 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 RECIST version 1.1
- Duration of objective response (DOR), 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
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by a blinded independent central review committee using RECIST v1.1, or death from any cause, whichever occurs first
- PFS in patients with baseline brain metastases as determined by investigator assessment using RECIST version 1.1
- OS in patients with baseline brain metastases defined as the time from randomization to death from any cause
- Central nervous system (CNS) PFS as determined by investigator assessment using RECIST version 1.1 in patients with or without baseline CNS metastases
- Mean absolute and mean change-from-baseline scores in function (Physical, Role) and global health status (GHS)/quality of life (QoL) as measured by the scales of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30)
- The proportion of patients with clinically meaningful deterioration in GHS/QoL physical, and role function as measured by scales of the EORTC QLQ-C30

Following the Sponsor's decision to prematurely terminate the study, analysis of PFS as determined by a blinded independent central review committee will no longer be conducted. Similarly, analysis based on the EORTC QLQ-C30 data will no longer be conducted.

EXPLORATORY EFFICACY OBJECTIVE

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

- Mean absolute and mean change-from-baseline scores in the remaining functions (Cognitive, Emotional, and Social), and disease- or treatment-related symptom scores of the EORTC QLQ-C30 and EORTC QLQ-Breast Cancer Module 23 Questionnaire (EORTC QLQ-BR23)

Following the Sponsor's decision to prematurely terminate the study, this exploratory efficacy objective is no longer applicable and corresponding analysis will no longer be performed.

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo 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 (NCI CTCAE) Version 5.0
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to evaluate the safety of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities (i.e., fatigue, chills, headache, cough, peripheral neuropathy, rash, aching muscles, aching joints, pain), as measured by the National Cancer Institute (NCI) Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument
- Change from baseline in symptomatic treatment toxicities, as measured by the PRO-CTCAE at pre-specified time points and an additional item regarding the overall burden experienced due to side effects of treatment from the EORTC item library

Following the Sponsor's decision to prematurely terminate the study, the exploratory safety objectives related to the PRO-CTCAE instrument are no longer applicable. The corresponding analyses will not be performed.

PHARMACOKINETIC OBJECTIVE

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

- To characterize the PK of trastuzumab emtansine when given in combination with atezolizumab
- To characterize the PK of atezolizumab when given in combination with trastuzumab emtansine

Following the Sponsor's decision to prematurely terminate the study, these objectives are no longer applicable. Accordingly, the corresponding analyses will not be performed.

IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab and trastuzumab emtansine when given in combination on the basis of the following endpoints:

- To characterize the prevalence and incidence of anti-drug antibodies (ADA) to atezolizumab in the presence of trastuzumab emtansine at pre-specified timepoints
- To characterize the prevalence and incidence of ADA to trastuzumab emtansine in the presence and absence of atezolizumab at pre-specified timepoints

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
- Following the Sponsor's decision to prematurely terminate the study, these objectives are no longer applicable. Accordingly, the corresponding analyses will not be performed.

BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to atezolizumab in combination with trastuzumab emtansine (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 and trastuzumab emtansine, 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 and/or trastuzumab emtansine activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Association of baseline immune status (may include but not limited to: protein, mRNA markers, T cell markers based on CD8 immunohistochemistry [IHC], and stromal tumor-infiltrating lymphocytes [TILs]) with efficacy
- Association of baseline HER2 expression level (protein and/or gene copy number/ratio) with efficacy
- Association of baseline PD-L1 expression level (≥1% and <5% IC vs ≥5% IC) with efficacy
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, tumor immunobiology, mechanisms of resistance

Following the Sponsor's decision to prematurely terminate the study, the objectives associated with efficacy are no longer applicable. Some descriptive analyses may be conducted as deemed appropriate.

HEALTH STATUS OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo on the basis of the following endpoint:

- Health utility and visual analog score (VAS) of the European Quality of Life 5-Dimension Questionnaire (5-level version; EQ-5D-5L) for pharmacoeconomic modeling at specified timepoints

Following the Sponsor's decision to prematurely terminate the study, these objectives are no longer applicable and the corresponding analyses will not be performed.

STUDY DESIGN

PREMATURE TERMINATION AND UNBLINDING AT STUDY LEVEL

The Sponsor has decided to prematurely terminate the study due to a lower-than-expected enrolment rate, which significantly extended the recruitment timelines. The investigators were informed of premature study termination on 15 December 2022 by a study memo communicating this decision.

Following a discussion between the investigator and the patient regarding the premature termination, the patient may consent to continue study treatment (i.e., either trastuzumab emtansine and atezolizumab or trastuzumab emtansine as a single agent; placebo will no longer be administered following unblinding of treatment assignment) if considered clinically appropriate by the investigator.

Patients should continue to receive study treatment and undergo the revised study assessments as described below:

Following the Sponsor's decision to prematurely terminate the study, tumor assessments will be conducted as per standard of care at the site.

After unblinding, patients will continue to be followed for tumor assessments until disease progression or until the patient discontinues from the study. All tumor assessments must be recorded in the eCRF. Tumor assessment scans will no longer be collected prospectively by the Sponsor as an independent review facility will not be utilized.

Blood samples will no longer be drawn for PK and ADA analyses or for biomarker analyses, as these analyses will no longer take place. Patient-Reported Outcome (PRO) assessments will also no longer be collected.

All safety assessments in the Schedule of Activities (Appendix 1) should be continued. All data should be recorded in the eCRF.

DESCRIPTION OF STUDY

This is a Phase III, randomized, multicenter, international, two-arm, double-blind, placebo-controlled clinical trial. The study will evaluate the efficacy, safety, pharmacokinetics, and patient-reported outcomes of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo in patients with HER2-positive and PD-L1-positive locally advanced (LABC) or metastatic breast cancer (MBC) who have progressed either during or after prior trastuzumab- (+/- pertuzumab) and taxane-based therapy for LABC/MBC, or during (or within 6 months after completing) trastuzumab- (+/- pertuzumab) and taxane-based therapy in the neoadjuvant and/or adjuvant setting. Previous adjuvant treatment with trastuzumab emtansine is not allowed if progression occurred during, or within 6 months after completing treatment.

HER2 positivity and PD-L1 positivity of the tumor tissues will be determined by a central laboratory. Patients whose tumors are not centrally determined to be both HER2-positive and PD-L1-positive will not be eligible.

Patients may be prescreened for HER2 and PD-L1 status at a central laboratory by participating in a separate prescreening consent.

Approximately 350 patients will be enrolled in the study at approximately 175 sites worldwide. Patients will be randomized into one of the following treatment arms in a 1:1 ratio by means of a permuted block randomization scheme through the use of an interactive Web or voice response system:

- Arm A: trastuzumab emtansine 3.6 mg/kg and placebo, q3w
- Arm B: trastuzumab emtansine 3.6 mg/kg and atezolizumab 1200 mg, q3w

Arm A and Arm B will be blinded with respect to administration of atezolizumab or placebo.

Crossover between treatment arms will not be permitted.

Randomization will be stratified according to:

- Local hormonal status (estrogen receptor [ER] and/or progesterone receptor [PgR] positive vs. ER and PgR negative/unknown),
- Disease status (visceral metastasis without brain metastasis vs. non-visceral metastasis only without brain metastasis [including locally advanced disease] vs. brain metastasis),
- World Region (Western Europe vs U.S. vs. Rest of World).

Patients must have measurable disease at baseline that is evaluable per RECIST v1.1. Patients must also have unresectable, locally advanced or metastatic disease. Locally advanced disease must not be amenable to resection or other local therapy with curative intent.

Patients will continue treatment until investigator-assessed radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or intolerable toxicity, whichever occurs first. Patients with isolated CNS progression that require local therapy only will be allowed to continue with study treatment as per investigator decision. These patients will be recorded as disease progression for PFS analysis but will remain blinded and continue with treatment as per initial randomization until further disease progression in whichever location, withdrawal of consent, death, or intolerable toxicity, whichever occurs first.

Patients will undergo scheduled tumor assessment every 6 weeks (± 7 days) that will continue until investigator-assessed radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who discontinue study treatment for reasons other than disease progression, even if they start new anti-cancer therapy, will continue to undergo tumor assessment every 6 weeks (± 7 days) until disease progression. Following the Sponsor's decision to prematurely terminate the study, tumor assessments will be conducted as per standard of care at the site.

Tumor response will be based on RECIST v1.1 for estimation of PFS, ORR, and DOR. Tumor assessment scans will be collected prospectively by an independent review facility. Response will also be assessed by a blinded independent central review committee. Following premature study termination, tumor assessment scans will no longer be collected prospectively by the Sponsor as an independent review facility will not be utilized.

Safety assessments will include the incidence, nature, 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.

Serum samples will be collected to monitor pharmacokinetics and to detect presence of antibodies to trastuzumab emtansine and atezolizumab. Tumor tissues, plasma and whole blood samples will be collected for exploratory biomarker assessments. Following the Sponsor's decision to prematurely terminate the study, samples for PK, ADA and exploratory biomarker research will no longer be collected..

Tumor tissue (historical sample or by new biopsy) will be collected at screening. A tissue sample from mandatory biopsy will be collected at the time of first evidence of radiographic disease progression per RECIST v1.1 (prior to the start of new anti-cancer treatment), unless not clinically feasible as assessed by the investigator. These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of trastuzumab emtansine in combination with atezolizumab.

After the Study Drug Completion Visit, all patients (regardless of reason for discontinuation) will be followed up for their survival status and new anti-cancer therapy every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. After patients discontinue from study treatment, information on subsequent anti-cancer therapies will be collected according to the same schedule as survival follow-up.

NUMBER OF PATIENTS

Approximately 350 patients will be enrolled in the study at approximately 175 sites worldwide. Following the Sponsor's decision to prematurely terminate the study, the objective of enrolling 350 patients will not be achieved.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by patient or legally-authorized representative
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically determined (*in a* central laboratory) HER2+/PD-L1+ LABC or MBC that is unresectable and previously treated with multimodality therapy:
  - Progression must have occurred during or after most recent treatment for LABC/MBC or during, or within 6 months after completing, neoadjuvant and/or adjuvant therapy
  - Prior treatment for breast cancer with trastuzumab (+/- pertuzumab) and taxane in the neoadjuvant and/or adjuvant, unresectable locally advanced, or metastatic settings
  - Patients must not have received more than two prior lines of therapy in the metastatic setting
  - Previous exposure to trastuzumab emtansine in the early breast cancer (EBC) setting is allowed only if disease recurrence occurred more than 6 months after completing, adjuvant trastuzumab emtansine. Previous exposure to trastuzumab emtansine in the metastatic setting is not allowed
  - Previous treatment with anti-HER2 agents (including, but not limited to, lapatinib, neratinib, tucatinib, trastuzumab deruxtecan, pyrotinib) and CD137 agonists, anti-programmed death−1 (PD-1), or anti-PD-L1 therapeutic antibody or pathway−targeting agents is allowed
  - Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible
  - Concurrent hormonal treatment for patients with hormone-positive disease is not allowed in the study

  - Localized palliative radiation therapy is allowed for symptom management if finalized before enrollment. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation. There is no required minimum recovery period
- Measurable disease per RECIST v1.1

    Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation
- Prospective central determination of representative tumor tissue specimen(s) prior to randomization of:
  - HER2-positive breast cancer as defined by an IHC score of 3+ or gene amplified by in situ hybridization (ISH) as defined by a ratio of ≥ 2.0 for the number of gene copies to the number of chromosome 17 copies
  - PD-L1 positivity defined by expression on tumor-infiltrating immune cells (IC) covering ≥ 1% of tumor area by IHC using the PD-L1 (SP142) assay
- For patients with bilateral breast cancer (synchronous or developed at a later stage), HER2 positivity must be centrally determined preferably in a metastatic biopsy or if not available in primary tumor from both left and right breast; at least one biopsy must be centrally determined as PD-L1 positive.
- For patients with initially multicentric tumors (multiple tumors involving more than one quadrant) or multifocal tumors (more than one mass confined to the same quadrant as the primary tumor), HER2 positivity must be centrally determined preferably in a metastatic biopsy or if not available in primary tumor, provided that:
  - For multicentric tumors all discrete lesions are centrally confirmed as HER2-positive and at least one lesion is centrally determined as PD-L1 positive
  - For multifocal tumors at least one focus is centrally confirmed as HER2-positive and PD-L1 positive
- A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 17 slides containing unstained, freshly cut, serial sections must be submitted (preferably along with an associated pathology report) prior to study enrollment. The unstained slides for staining must be within the current documented cutslide stability window. The sample needs to be of good quality based on total and viable tumor content. If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening. A biopsy may also be performed at screening if a patient's archival tissue test results do not meet eligibility criteria.

    Cytological or fine-needle aspiration samples and bone specimens are not acceptable for central testing to determine eligibility.
- Willing to provide blood samples before treatment start, while on-study, and at progression, for standard of care follow-up and exploratory research on biomarkers
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Life expectancy ≥ 6 months
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 7 days prior to initiation of study treatment:
  - ANC ≥ 1.5 x 10^9/L (≥ 1500/µL) without granulocyte colony-stimulating factor support
  - Lymphocyte count ≥ 0.5 x 10^9/L (≥ 500/µL)
  - Platelet count ≥ 100 x 10^9/L (≥ 100,000/µL) without transfusion
  - Hemoglobin ≥ 90 g/L (≥ 9 g/dL)

    Patients may be transfused to meet this criterion

- AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 x upper limit of normal (ULN), with the following exceptions:

  Patients with documented liver metastases: AST and ALT ≤ 5 x ULN

  Patients with documented liver or bone metastases: ALP ≤ 5 x ULN
- Total bilirubin ≤ 1.5 x ULN with the following exception:

  Patients with known Gilbert disease: total bilirubin ≤ 3 x ULN
- Creatinine ≤ 1.5 x ULN or Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
- Albumin ≥ 25 g/L (≥ 2.5 g/dL)
- For patients not receiving therapeutic anticoagulation: INR and aPTT ≤ 1.5 x ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen

- Negative HIV test at screening
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, 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 7 months after the final dose of study treatment. 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 is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential. 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, hormonal contraceptives that inhibit ovulation, and hormone-releasing intrauterine devices and copper intrauterine devices; 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

If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form

- 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 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 7 months after the final dose of study treatment. Men must refrain from donating sperm during this same period

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 7 months after the final dose of study treatment 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

If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form

Exclusion Criteria

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

- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (for complications of infections or relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1

  This also applies to patients with suspected or confirmed COVID-19 infection
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study
- 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
- Prior treatment with trastuzumab emtansine in metastatic setting
- 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
- Symptomatic or actively progressing central nervous system (CNS) metastases

  Asymptomatic CNS lesions ≤ 2cm without clinical requirement for local intervention (whole brain radiation therapy and/or stereotactic radiosurgery and/or surgery) are eligible, provided that all of the following criteria are met; it is for investigator to decide if local intervention is indicated

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS
  - No brain lesions thought to require immediate local therapy
  - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage
  - The patient has not undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 21 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment
  - Anticonvulsant therapy at a stable dose is permitted

    No ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or

equivalent). Subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) are eligible

Note: Patients with new asymptomatic CNS metastases detected at the screening scan who require radiation therapy and/or surgery for CNS metastases, must receive it before screening. Following local intervention, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- History of leptomeningeal disease
- 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
- Uncontrolled tumor-related pain

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

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated ≥ 14 days prior to Cycle 1, Day 1. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to study treatment initiation

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium greater than ULN)
- Current Grade ≥ 3 peripheral neuropathy (according to the NCI CTCAE v5.0)
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HbsAg] test at screening) or hepatitis C

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

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
- Current treatment with anti-viral therapy for HBV
- 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, anti-phospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, 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

        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        - There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months
        - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- 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 CT scan

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted
- Active tuberculosis
- Cardiopulmonary dysfunction as defined by:
    - Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg with or without medication)
    - Inadequate left ventricular ejection fraction at baseline, < 50% by either ECHO or MUGA
    - History of symptomatic congestive heart failure (CHF)-Grade ≥ 3 per NCI CTCAE version 5.0 or Class ≥ II New York Health Association
    - History of a decrease in left ventricular ejection fraction to < 40% or symptomatic CHF with prior trastuzumab treatment
    - Myocardial infarction or unstable angina within 6 months of randomization
    - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
    - Evidence of transmural infarction on ECG
    - Significant symptoms (Grade ≥ 2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia
    - High-risk uncontrolled arrhythmias (i.e., supraventricular 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])
- Major surgical procedure, other than for diagnosis, or significant traumatic injury within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy within 5 years prior to initiation of study treatment, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 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
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
- 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, 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 treatment or within 5 months after the final dose of study treatment
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (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-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:
  - 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
  - Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study
- 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
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the trastuzumab emtansine formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within 7 months after the last dose of study treatment

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

END OF STUDY

The end of study is planned to occur after approximately 184 OS events are obtained (approximately 40 months after the primary efficacy analysis of PFS [and concurrent first interim analysis of OS]). The end of this study is defined as the date when the last patient, last visit occurs, or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

The Sponsor has decided to prematurely terminate the study due to a lower-than-expected enrolment rate. The investigators were informed of this decision on 15 December 2022. Patients have the option to remain on the study and continue treatment until arrangements are put in place for continuing treatment on an extension study (BO25430) or in a Post-Trial Access Program or other local options. The treatment solution for each patient may vary, taking into account local regulations and requirements.

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 78.1 months. The length of study will now be determined by the time taken at each study site to implement the off-study patient treatment solutions, which should be approximately by the end of 2023.

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 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 (or in the 3 days prior) 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 for trastuzumab emtansine. 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.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Dose reductions for atezolizumab are not allowed during this study.

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.

Atezolizumab or placebo will be administered first, followed by trastuzumab emtansine.

COMPARATOR

Placebo will be administered IV according to the same schedule as atezolizumab.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

None.

STATISTICAL METHODS

PRIMARY ANALYSIS

The multiple primary efficacy endpoints for this study are PFS based on investigator tumor assessment and OS. The ITT population is the primary analysis population for the primary efficacy endpoints 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.

The primary PFS analysis (and first interim OS analysis) is planned to be performed when approximately 229 PFS events had occurred. It is expected to have approximately 87 OS events at that point in time. The estimated time from first-patient-in to primary PFS/first interim OS analysis is approximately 38 months.

Following the Sponsor's decision to prematurely terminate the study, there will be only a single analysis timepoint for both PFS and OS primary efficacy endpoints. Interim analyses will no longer be conducted. Considering the expected lack of maturity of the data, the analysis of PFS and OS primary efficacy endpoints will only be reported in a descriptive way. No formal testing will be performed and no control for the overall type I error (α) accounting for the two primary endpoints will be implemented. Consequently, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

PROGRESSION-FREE SURVIVAL

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.

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 the factors specified in the protocol (excluding world region) will be used to compare PFS between the treatment arms. If less than 5 events are observed in any combination, only the unstratified analysis will be done. 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 will be used to estimate the HR and to calculate the 95% CI of the HR.

In order to assess the consistency of treatment benefit with respect to the multiple primary efficacy endpoints PFS and OS 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 HER2 and PD-L1 expression, ECOG status, hormone receptor status, and line of treatment in the metastatic setting (first or second line vs. third line).

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 PFS. The 2-sided log-rank test, stratified by the factors specified in the protocol (excluding world region) will be used to compare OS between the treatment arms.

DETERMINATION OF SAMPLE SIZE

The two primary efficacy endpoints for this study are PFS based on investigator tumor assessment and OS.

This study has been designed to detect a substantial magnitude of benefit in the ITT population, that is, improvement in median PFS from 7 months in the control arm to 11.67 months in the experimental arm, corresponding to a target PFS hazard ratio of 0.60, and improvement in median OS from 31 months in the control arm to 47.7 months in the experimental arm, corresponding to a target OS hazard ratio of 0.65.

Approximately 350 patients randomized according to a 1:1 randomization (approximately 175 patients will be randomized to Arm A and to Arm B) will be enrolled in the study. The sample size assumes an annual dropout rate of 10% in both treatment arms and result in an estimated recruitment time of about 32 months (with ramp up in the first 8 months). Following the Sponsor's decision to prematurely terminate the study, the initially planned number of randomized patients will not be reached.

Furthermore, in the context of premature study termination, there will be only a single analysis timepoint for the PFS and OS primary efficacy endpoints. Interim analyses will no longer be conducted. Considering the expected lack of maturity of the data the analysis of PFS and OS primary efficacy endpoints will only be reported in a descriptive way. No formal testing will be performed and no control for the overall type I error (α) accounting for the two primary endpoints will be implemented. Consequently, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

INTERIM ANALYSES

Following the Sponsor's decision to prematurely terminate the study, the interim analyses will no longer be conducted.

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