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: Protocol Version 4: 02-March-2023

PROTOCOL

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)
MEDICAL MONITOR:	[redacted] MD
SPONSOR:	F. Hoffmann-La Roche Ltd

APPROVAL: See electronic signature and date stamp on the final page of this document

PROTOCOL HISTORY

Protocol		Associated Country-and/or Region-Specific Protocol		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
4	See electronic date stamp on the final page of this document	—		
3	24 February 2022	—	3	
2	15 March 2021	Germany	2	8 October 2021
1	17 September 2020	VHP	1	7 December 2020

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol MO42319 has been amended to include the Sponsor's decision to prematurely terminate the study due to low enrollment rate and to align with the atezolizumab Investigator's Brochure (Version 19, and Addenda 1 and 2). Several aspects of the study design have also been clarified. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

The following changes have been made following on the Sponsor's decision to prematurely terminate the study:

- Revisions have been made to the study objectives to indicate which objectives are no longer applicable and the corresponsing analyses that will no longer be performed (Section 2 and Section 6).

- Section 3.1 has been updated with the decision to unblind the study.

- Section 3.2 has been added to provide the rationale for unblinding and the implications of unblinding on the study design and assessments.

- Section 3.2.1 has been added to provide further guidance on revised study assessments following the decision to prematurely terminate the study; the schedule for tumor assessments may now be carried out as per the standard of care at the study site. Blood samples no longer need to be collected for biomarker, pharmacokinetic (PK), and anti-drug antibody (ADA) analyses. Patient-reported outcome (PRO) assessments also no longer need to be completed.

- It has been clarified that the objective of enrolling 350 patients will not be achieved (Section 3.3).

- The end of study and length of study have been updated. It is clarified that time to closure of study sites may vary locally (Section 3.4).

- Section 4.3.5, Continued Access to Trastuzumab Emtansine and Atezolizumab has been updated with information on continued access treatment options for patients who are still on treatment, either as part of an extension study (BO25430) or as part of a post-trial access program. The treatment solution for each patient may vary, taking into account local regulations and requirements.

- Wording has been amended to clarify that vital sign readings should be taken before and after each infusion of trastuzumab emtansine (Section 4.5.4 and Table 4).

- Tumor and response evaluations have been updated to state that tumor assessments may now be performed as per the study site's standard of care, and are no longer required to be done every 6 weeks (Section 4.5.5.)

- Tumor assessment scans will no longer be collected prospectively by the Sponsor as an independent review facility will not be utilized (Section 4.5.5.2).

- Sections on sample collection have been updated to clarify that biomarker and other biological samples are no longer required to be collected (Section 4.5.7 and Appendix 2).

- Clinical outcome assessments have been updated to clarify that PRO assessments no longer need to be collected (Section 4.5.9 and Appendix 3).

- Wording on discontinuations is updated to require that patients in follow-up have a final site visit and check that any ongoing AEs have resolved before discontinuation from the study (Section 4.6.1).

- A statement has been added that the investigators were informed of premature study termination on 15 December 2022 (Section 4.6.3).

- Information on risks associated with trastuzumab emtansine has been updated with guidance for pneumonitis and ILD toxicities that are Grade 1 – 2 (Section 5.1.1.1).

- The planned analyses for both PFS and OS in the context of the premature study termination have been clarified, as well as the impact of the premature study termination on the study sample size (Section 6.1).

- Sections 6.4 through 6.9 (Efficacy Analyses through Health Status Utility Analyses) have been updated to account for the revisions made to the study objectives following the Sponsor's decision to prematurely terminate the study.

- Clarification has been added that an interim analysis is no longer planned given that the study is being prematurely terminated (Section 6.10).

- Appendix 1, Schedule of Activities, has been updated with the recommendation to perform additional laboratory tests in Follow-up (footnote [ff]) and with revised sample collection guidance as per Sections 4.5.5, 4.5.7, and 4.5.9.

The protocol has been updated to align with the Atezolizumab Investigator's Brochure, Version 19, and with Addendum 1 and 2, as follows:

- The medical term “Wegener granulomatosis” has been replaced by the term “granulomatosis with polyangiitis” to align with the updated preferred term in MedDRA (Section 4.1.2 and Appendix 15)

- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly. The list of identified risks for atezolizumab has been revised to include myelitis , facial paresis, and pericardial disorders (Section 5.1.2).

- Myelitis and facial paresis have been added to adverse events of special interest for atezolizumab (Section 5.2.3).

- Appendix 15 has been revised to include autoimmune myelitis

- Appendix 19 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.

- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19, and with Addendum 1 and 2.

The following additional changes have been made to Appendix 20:

- The option to continue treatment with trastuzumab alone and the provision of trastuzumab has been removed as this was added in error to the previous protocol version.
- Management guidelines for pneumonitis and ILD (Table 1) have been updated to permit continuation of treatment with trastuzumab emtansine if the adverse event is Grade 1 —2 and if resolved within 42 days, at the same dose level for Grade 1 and at one dose-level reduction for Grade 2 toxicities

The following administrative changes have been made:

- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.11.6)
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Clinical Trials Regulation requirements (Section 8.4).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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
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MEDICAL MONITOR:	[redacted] [redacted] MD
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

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)**
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IND NUMBER:	71,072
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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 (a) 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 $\geq$ 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, theanalysis 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 (a) 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 (a) 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
BC	breast cancer
BFI	Brief Fatigue Inventory
BUN	blood urea nitrogen
CBC	complete blood count
CCOD	clinical cut-off date
CHF	congestive heart failure
CI	confidence interval
Cmax	maximum serum concentrations observed
Cmin	minimum serum concentration under steady-state conditions within a dosing interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	*coronavirus disease 2019*
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome p450

Abbreviation	Definition
DM1	N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (the thiol-containing maytansinoid anti-microtubule agent conjugated to trastuzumab in trastuzumab emtansine)
DMC	Data Monitoring Committee
DOR	duration of response
EBC	early breast cancer
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-level version
ER	estrogen receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
GHS	global health status
HER2	human epidermal growth factor 2
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBV/HCV	hepatitis B virus/ hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
IC	tumor-infiltrating immune cell
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Center
IFNγ	interferon gamma

Abbreviation	Definition
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRF	Independent review facility
IRR	infusion-related reactions
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous(ly)
IxRS	interactive voice or web-based response system
LABC	locally advanced breast cancer
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAS	macrophage activation syndrome
MBC	metastatic breast cancer
MDASI	MD Anderson Symptom Inventory
MHC1	major histocompatibility complex class 1
MRI	magnetic resonance imaging
MUGA	multigated acquisition (scan)
nab-paclitaxel	protein-bound paclitaxel
NCCN	National Comprehensive Cancer Network
NIMP	non-investigational medicinal product
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NRH	nodular regenerative hyperplasia
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	pharmacokinetic
PO	orally
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient Reported Outcomes Common Terminology Criteria for Adverse Events
q2w	every 2 weeks
q3w	every 3 weeks
QLQ-C30	quality-of-life questionnaire for cancer
QoL	quality of life
RBC	red blood cell
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
rh-TPO	human recombinant thrombopoeitin
SAE	serious adverse events
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
SLD	sum of the longest diameters
SC	Steering Committee
TC	tumor cell
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor alpha
TPC	treatment of physician’s choice
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE METASTATIC BREAST CANCER

Breast cancer is the most common cancer among women in the world with an estimated 2.1 million cases diagnosed globally per year and approximately 627,000 deaths (Bray et al. 2018). While advances in early diagnosis and adjuvant therapy have led to a decrease in mortality rates from breast cancer in developed countries, the prevalence of metastatic breast cancer (MBC) is still high. MBC is not considered curable and median overall survival (OS) ranges from approximately 1 year to approximately 5 years, depending on subtype (Waks and Winer 2019). Numerous cytotoxic chemotherapy agents have demonstrated anti-tumor activity for MBC, including anti-tubulin drugs. Treatment choices are generally guided by disease characteristics (i.e., HER2/hormone receptor status of the disease, number and specific location of metastatic sites, treatment history in both adjuvant and metastatic settings), the toxicity of the potential treatments, the physical well-being of the patient, as well as physician and patient preferences. The main goals of treatment are to improve patients' quality of life and prolong survival (Gennari et al. 2021).

Human epidermal growth factor receptor 2 (HER2), also known as erbB2, neu, and p185HER2, represents a prominent target in breast cancer with approximately 15%−20% of patients with primary invasive breast cancers overexpressing the HER2 receptor (Reese and Slamon 1997; Owens et al. 2004; Wolff et al. 2013; Zhang et al. 2015). In the absence of HER2-targeted therapy, primary breast cancers that overexpress HER2 are associated with a poorer prognosis, including a greater risk of relapse and shortened survival compared with that of HER2 normal tumors (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001).

Since its first approval in 1998, the combination of trastuzumab and a taxane was widely accepted as the first-line treatment option of choice for patients with HER2-positive MBC on the basis of the survival advantage demonstrated in two large pivotal trials (Studies H0648g [Slamon et al. 2001] and M77001 [Marty et al. 2005]). The regimen of pertuzumab in combination with trastuzumab and docetaxel has shown clear superiority in terms of both progression-free survival (PFS) and OS with a generally similar safety profile (Study WO20698/TOC4129g [Baselga et al. 2012]) and is the standard of care in many countries.

For second-line treatment of MBC, trastuzumab emtansine was established as the standard of care, based on the results of the EMILIA study (TDM4370g/BO21977; see Section 1.2.1). Data from the DESTINY-Breast 03 trial are likely to result in trastuzumab deruxtecan becoming the new standard of care second-line therapy in regions where this drug is available, moving trastuzumab emtansine potentially to the third line setting (Gennari et al. 2021; National Comprehensive Cancer Network [NCCN] 2021a). Several

other treatment options are available for further lines of therapy in MBC (Gennari et al. 2021; Giordano et al. 2018), including tucatinib which was recently approved in combination with trastuzumab and capecitabine for use in patients with HER2-positive MBC who have received one or more prior anti-HER2-based regimens in the metastatic setting (NCCN 2021a).

Although the treatment of MBC is palliative rather than curative in intent, improvement in survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and acceptable toxicity, which can be combined with established treatments for breast cancer.

1.2 BACKGROUND ON TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (Kadcyla®) is an antibody-drug conjugate (ADC). Linkage of a cytotoxic agent to highly specific monoclonal antibodies targeting unique and/or overexpressed cell-surface tumor antigens focuses the delivery of such agents to tumor cells (TCs), creating a more favorable therapeutic window than can be achieved by their administration as free drugs. Trastuzumab emtansine is specifically designed for the treatment of HER2-positive cancer. It is composed of the cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent; N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine) conjugated to trastuzumab via lysine side chains, with an average drug-to-antibody ratio of approximately 3.5:1.

Trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. After binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity.

Phase I, II, and III studies of trastuzumab emtansine have demonstrated clinical activity when trastuzumab emtansine is given as a single agent to patients with HER2-positive MBC who have progressed on a trastuzumab-containing regimen. In patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane, trastuzumab emtansine has significantly prolonged PFS and OS with a more favorable safety profile than lapatinib plus capecitabine (Study BO21977/TDM4370g, EMILIA [Verma et al. 2012; Diéras et al. 2017]) or compared to a treatment of physicians' choice in patients who previously received trastuzumab, taxane and lapatinib (Study BO25734/TDM4997g, TH3RESA [Krop et al. 2014; Krop et al. 2017]). Single-agent trastuzumab emtansine is also active in the HER2-positive early breast cancer (EBC) setting (von Minckwitz et al. 2019).

Data from clinical trials of trastuzumab emtansine that are relevant to the design of the current trial are summarized in Section 1.2. Refer to the most recent version of the trastuzumab emtansine Investigator's Brochure for further information on all of the completed and ongoing trastuzumab emtansine studies.

1.2.1 Study TDM4370g/BO21977 (EMILIA)

Study TDM4370g/BO21977 (EMILIA) was a randomized Phase III study of trastuzumab emtansine versus lapatinib plus capecitabine in patients with HER2-positive, unresectable locally advanced breast cancer (LABC) or MBC previously treated with trastuzumab and a taxane (n = 991). Patients received trastuzumab emtansine (3.6 mg/kg intravenously [IV] every 3 weeks [q3w]) or capecitabine (1000 mg/m^2 orally [PO] twice daily, Days 1−14 q3w) plus lapatinib (1250 mg PO daily) until progressive disease (PD) or unmanageable toxicity.

Primary endpoints were PFS by independent review, OS, and safety. An interim OS analysis was planned at the time of the final PFS analysis. A total of 991 patients were enrolled, and 978 patients received treatment. Baseline patient demographics, prior therapy, and disease characteristics were balanced. There was a significant improvement in PFS favoring trastuzumab emtansine (hazard ratio [HR] = 0.650, 95% confidence interval [CI] = 0.549, 0.771; $p < 0.0001$; median: 9.6 vs.6.4 months). Objective response rate (ORR) was 43.6% for the trastuzumab emtansine arm versus 30.8% for the lapatinib plus capecitabine arm, with a median duration of response (DOR) of 12.6 months versus 6.5 months, respectively (Verma et al. 2012).

Trastuzumab emtansine was well tolerated, with no unexpected safety signals at the time of the primary analysis. The most common Grade ≥ 3 adverse events (Aes) in the trastuzumab emtansine arm were thrombocytopenia (12.9% vs. 0.2%, respectively), increased aspartate aminotransferase (AST) (4.3% vs. 0.8%), and increased alanine aminotransferase (ALT) (2.9% vs. 1.4%); the most common Grade ≥ 3 Aes in the lapatinib plus capecitabine arm were diarrhea (20.7% vs. 1.6%), palmar plantar erythrodysesthesia (16.4% vs. 0%), and vomiting (4.5% vs. 0.8%). The incidence of Grade 3 Aes in the trastuzumab emtansine arm was 40.8% versus 57.0% in the lapatinib plus capecitabine arm (Verma et al. 2012).

A second Interim analysis for OS demonstrated that the co-primary endpoint of OS was met. OS was significantly improved in patients receiving trastuzumab emtansine, with a 31.8% reduction in the risk of death associated with trastuzumab emtansine compared with lapatinib and capecitabine (HR = 0.682, 95% CI: 0.548, 0.849; $p = 0.0006$). The median duration of survival was 25.1 months in patients treated with lapatinib plus capecitabine, compared with 30.9 months in patients treated with trastuzumab emtansine (Verma et al. 2012).

The final descriptive OS analysis showed a consistent survival benefit for trastuzumab emtansine compared with lapatinib plus capecitabine (median OS 29.9 vs 25.9 months, stratified HR = 0.75), despite 27% of patients crossing over from the control arm to trastuzumab emtansine. The safety profile of trastuzumab emtansine remained largely consistent between the time of the primary, second interim and final OS analyses, with a median follow-up time of 48 months in the final analysis (Diéras et al. 2017).

1.2.2 Study TDM4997g/BO25734 (TH3RESA)

Study TDM4997g/BO25734 (TH3RESA) was a Phase III, randomized, open-label trial to evaluate trastuzumab emtansine compared with treatment of physician's choice (TPC; these were approved or standard of care therapies based on frequently-used regimens) in patients with HER2-positive MBC. Patients had received prior treatments with trastuzumab, lapatinib, and a taxane in any setting, and disease progression occurred after at least two regimens of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting.

Analysis of the co-primary efficacy endpoints of PFS per investigator assessment and the first OS interim analysis, plus all secondary efficacy endpoints, was based on a data cutoff date of 11 February 2013 (Krop et al. 2014). The study demonstrated a statistically significant and clinically meaningful improvement in PFS for trastuzumab emtansine compared with TPC. The median PFS for trastuzumab emtansine was 6.2 months and for TPC 3.3 months with a stratified HR = 0.528 (95% CI: 0.422, 0.661); $p < 0.0001$. The ORR was 31% for the trastuzumab emtansine arm versus 9% for the TPC arm, with a median DOR of difference 22.7% [95% CI: 16.2, 29.2]; $p < 0{\cdot}0001$). The median DOR was 9.7 months (95% CI: 6.6, 10.5) in the trastuzumab emtansine group, but it had not been reached at the data cutoff in the patients with an objective response in the physician's choice group.

Interim OS analysis showed a trend favoring trastuzumab emtansine (stratified HR = 0.552 [95% CI: 0.369, 0.826]; p = 0.0034), but the stopping boundary was not crossed. Fewer patients receiving trastuzumab emtansine than those receiving TPC had Grade ≥ 3 aEs (32.3% vs. 43.5%). Grade ≥ 3 aEs reported in at least 2% of patients receiving trastuzumab emtansine were: thrombocytopenia (4.7%), anemia (2.7%), neutropenia (2.5%), AST increased (2.2%), fatigue (2.0%), and dyspnea (2.0%) (Krop et al. 2014).

At the second OS interim analysis, which constituted the final OS analysis, trastuzumab emtansine demonstrated a clinically meaningful and statistically significant improvement in OS compared with TPC. The median OS improved from 15.8 months (TPC) to 22.7 months (trastuzumab emtansine (stratified HR 0.58 [95% CI: 0.43, 0.71]; p = 0.0002). Despite the longer treatment duration relative to control (4.1 months; [0.03 – 31.2)], trastuzumab emtansine (7.9 months [0.03 – 38] had a favorable safety profile which was consistent with prior studies (Krop et al. 2017).

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of

tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent therapy in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non-small cell lung cancer (NSCLC), hepatocellular cancer, small-cell lung cancer, melanoma, and triple-negative breast cancer (TNBC). Differences in approval may exist across countries.

For details on nonclinical studies and clinical studies evaluating atezolizumab monotherapy and in combination with other agents, and in other indications, refer to the Atezolizumab Investigator's Brochure.

1.3.1 Study GO29831

Study GO29831 is a completed Phase Ib open-label, multi-cohort study evaluating the safety, tolerability, and pharmacokinetics of atezolizumab in combination with trastuzumab emtansine or with trastuzumab and pertuzumab (with or without chemotherapy agents) in patients with HER2-positive MBC, treatment-naive patients with operable LABC, or inflammatory EBC. HER2-negative patients were also eligible for one cohort only. The primary objective for this study was to evaluate the safety and tolerability of the following combination treatments:

- Atezolizumab + trastuzumab + pertuzumab or atezolizumab + trastuzumab emtansine in patients with HER2-positive MBC or patients who are treatment-naive with operable LABC or inflammatory EBC
- Atezolizumab + trastuzumab + pertuzumab + docetaxel in patients with HER2positive MBC
- Atezolizumab + doxorubicin + cyclophosphamide in patients with HER2-negative MBC

A total of 76 patients were enrolled and treated in this two-stage study: 36 patients with MBC and 40 patients with LABC/EBC. Of these, 40 patients were treated with trastuzumab emtansine (3.6 mg/kg q3w) plus atezolizumab (1200 mg q3w).

- 6 patients with MBC in the safety evaluation stage (Cohort 1B)
- 14 patients with MBC in a safety expansion cohort (Cohort 2C)
- 20 patients with LABC/EBC in the neoadjuvant window stage (Cohort 2B)

Confirmed responses by RECIST v1.1 were seen in both MBC cohorts (Cohort 1B: one CR and one PR [ORR: 33%]; Cohort 2C: one CR and 4 PR [ORR: 35.7%]). Confirmed response rates per immune-modified RECIST (imRECIST) were consistent with those reported using standard RECIST. The pathologic complete response (pCR) rate in Cohort 2B was 14/20 (70%; 95% CI: 46, 88).

AEs in Cohort 1B (n=6) occurring in more than one patient comprised fatigue (83.3%), nausea, thrombocytopenia (each 50%), asthenia, pneumonia and anemia (each 33.3%). AEs in Cohort 2C (n=14) occurring in >20% of patients comprised fatigue (64.3%), decreased appetite (50.0%), chills, pyrexia, headache, anemia, cough, constipation (42.9%), nausea, dry mouth, upper respiratory tract infection, vomiting (35.7%), diarrhea, urinary tract infection, pneumonia, dyspnea, back pain, aspartate aminotransferase increased (28.6%), nasopharyngitis, thrombocytopenia, epistaxis, hypomagnesemia, bone pain, platelet count decreased (21.4%). The most frequent AEs in Cohort 2B were: diarrhea, fatigue (75.0%), nausea (70.0%), anemia, constipation (45%), headache, epistaxis, decreased appetite, hypomagnesemia (40%), hypokalemia, alopecia (35%), mucosal inflammation (30%), peripheral edema, neutropenia, thrombocytopenia, dehydration, rash, increased AST, and ALT (25%).

One (16.7%) patient in Cohort 1B discontinued treatment due to an AE (Grade 4 hypercalcemia) and two (14.3%) patients in Cohort 2C (Grade 2 increased AST and Grade 2 interstitial lung disease). Four (20.0%) patients in Cohort 2B discontinued treatment due to an AE (Grade 5 AE of death, Grade 3 AEs of transaminase increased, diarrhea and Grade1 or 2 AEs of chest pain, dyspnea and dehydration.

Grade ≥3 AEs occurring in more than one patient in Cohort 1B were thrombocytopenia and pneumonia; in Cohort 2C only pneumonia occurred in more than one patient (n = 2 [14.3%]). No fatal AEs occurred in Cohorts 1B and 2C. Grade ≥3 AEs occurring in more than one patient on Cohort 2B were anemia, neutropenia, thrombocytopenia, diarrhea, hypokalemia, hypomagnesemia, increased transaminase, peripheral neuropathy, mucosal inflammation, and hypertension.

1.3.2 Study WO30085 (KATE2)

Study WO30085 is a completed randomized, multicenter, double-blind, placebo-controlled Phase II study of the efficacy, safety, and pharmacokinetics of trastuzumab emtansine in combination with atezolizumab or placebo (atezolizumab/placebo) in patients with HER2-positive, LABC or MBC, who have received prior trastuzumab and taxane based therapy, either alone or in combination, and/or who have progressed during, or within 6 months after completing, adjuvant therapy.

Patients were randomized (2:1) to receive trastuzumab emtansine (3.6 mg/kg) combined with atezolizumab (1200 mg) or placebo, given intravenously every 3 weeks. Randomization was stratified by PD-L1 immunohistochemistry (IHC) status, world region, and presence/absence of liver metastases. The treatment arms were generally

well balanced at baseline, except that the proportion of patients with an ECOG performance status of zero was numerically higher in the combination therapy arm (70% vs 58%).

The primary efficacy objective for this study was to evaluate the efficacy of the combination of trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo as measured by investigator-assessed PFS. The primary PFS analysis was planned for when approximately 115 PFS events had occurred. Secondary efficacy endpoints were OS, ORR (according to RECIST v1.1), and 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.

On 22 November 2017, the iDMC met and conducted a pre-planned benefit–risk analysis. Following this analysis, the iDMC recommended to the Sponsor that the study be unblinded with respect to treatment assignment. This recommendation was based on the following factors:

- Improbability of meeting the PFS endpoint
- Numerically higher rates of SAEs that included one fatal event (hemophagocytic syndrome) in the atezolizumab arm
- Numerically higher AEs leading to discontinuation of study drugs in the atezolizumab arm.

As of the clinical cut-off date (CCOD) of 11 December 2017, 202 patients had been randomized in a 1:2 ratio, comprising the ITT population (69 patients in the trastuzumab emtansine plus placebo arm and 133 patients in the trastuzumab emtansine plus atezolizumab arm).

The study did not demonstrate a clinically meaningful PFS benefit from the addition of atezolizumab to trastuzumab emtansine in the ITT population. The stratified HR was 0.82 (95% CI: 0.55, 1.23; $p = 0.3332$). The median PFS for trastuzumab emtansine plus placebo was 6.8 months (95% CI: 4.0, 11.1) and for the trastuzumab emtansine plus atezolizumab was 8.2 months (95% CI: 5.8, 10.7) (Emens et al. 2019a).

At the final analysis (CCOD: 11 December 2018), 52 OS events were reported (20 [29.0%] deaths in the trastuzumab emtansine plus placebo arm and 32 [24.1%] deaths in the trastuzumab emtansine plus atezolizumab arm) (Emens et al. 2019b). Median OS was not reached in either arm (stratified HR = 0.74 [95% CI: 0.42, 1.30] and 1-year OS was similar (89.0% with trastuzumab emtansine plus placebo and 89.1% with trastuzumab emtansine plus atezolizumab).

At the primary analysis (CCOD: 11 December 2017; Report No. 1087133), the safety profile of the combination of trastuzumab emtansine and atezolizumab was consistent

with the known profiles of each study drug, and AEs for the combination were manageable. The proportion of patients experiencing AEs was similar between the two arms: 95.6% of patients receiving trastuzumab emtansine plus placebo, and 99.2% of patients receiving trastuzumab emtansine plus atezolizumab had at least one AE. Despite higher rate of SAEs in the trastuzumab emtansine plus atezolizumab arm, the overall incidence of Grade ≥3 AEs was similar between the two arms (Table 1).

The most common Grade ≥3 AEs (in at least 4% of patients) in patients receiving trastuzumab emtansine plus atezolizumab were thrombocytopenia (12.9%), AST increased (8.3%), anemia (5.3%), ALT increased, and neutropenia (4.5% each). The most common Grade ≥3 AEs (in at least 4% of patients) in patients receiving trastuzumab emtansine plus placebo were thrombocytopenia, neutropenia, and urinary tract infection (all 4.4% each). All other Grade ≥3 AEs occurred in <4% of patients in each arm.

Table 1 KATE2 Safety Profile According to Study Arms

Patients with	T-DM1 + Placebo (N=68) [Grade 3-4]	T-DM1 + Atezo (N=132) [Grade 3-4]
AE leading to death	0	1 (0.8%) *
SAE	13 (19.1%)	43 (32.6%)
AE Grade ≥3	28 (41.2%)	58 (43.9%)
AE leading to T-DM1 discontinuation	9 (13.2%)	20 (15.2%)
AE leading to T-DM1 dose reduction/interruption	13 (19.1%)	46 (34.8%)
AE leading to atezolizumab/placebo discontinuation	10 (14.7)	33 (25.0)
AE leading to atezolizumab/placebo interruption	14 (20.6)	54 (40.9)
Hepatotoxicity	16 (23.5%) [4 (5.9%)]	44 (33.3%) [14 (10.6%)]
Cardiac dysfunction	4 (5.9%) [0]	1 (0.8%) [0]
Thrombocytopenia	9 (13.2%) [3 (4.4%)]	38 (28.8%) [13 (9.8%)]
IRR/Hypersensitivity Type I	22 (32.4%) [0]	66 (50%) [5 (3.8%)]
Pulmonary Toxicity	3 (4.4%) [1 (1.5%)]	6 (4.5%) [1 (0.8%)]
Peripheral neuropathy	16 (23.5%) [2 (2.9%)]	39 (29.5%) [3 (2.3%)]
Hemorrhage	15 (22.1%) [1 (1.5%)]	33 (25%) [2 (1.5%)]

AE = adverse event; IRR = infusion-related reaction; T-DM1 = trastuzumab emtansine.
*histiocytosis hematophagic.

Hepatotoxicity was mostly Grade 1 or 2 and the most commonly reported AEs were increased AST and increased ALT. Grade ≥3 hepatoxicity AEs were reported in 4 (5.9%) patients in the trastuzumab emtansine plus placebo arm and 14 (10.6%) patients in the trastuzumab emtansine plus atezolizumab arm; one event in each group was a Grade 4 AE. No patients from the trastuzumab emtansine plus atezolizumab arm fulfilled the Hy's Law criteria and there were no deaths due to hepatotoxicity in the study.

The majority of cases of thrombocytopenia in the atezolizumab arm were reported as non-serious. Grade ≥3 thrombocytopenia was reported in 3 (4.4%) patients in the trastuzumab emtansine plus placebo arm (none of which were Grade 4) and 13 (9.8%) patients in the trastuzumab emtansine plus atezolizumab arm (5 [3.8%] of which were with Grade 4 events). The higher incidence of thrombocytopenia in the trastuzumab emtansine plus atezolizumab arm did not lead to increased hemorrhage (Table 1).

The difference in IRR/hypersensitivity in the two arms was mainly driven by pyrexia occurring during infusion or within 24 hours.

Fewer patients (8.8%) in the trastuzumab emtansine plus placebo arm had AEs that led to dose reduction of trastuzumab emtansine compared to patients (16.7%) in the trastuzumab emtansine plus atezolizumab arm. The most common AEs leading to trastuzumab emtansine dose reduction were thrombocytopenia (2.9% vs. 6.8%) and AST/ALT increase (both 1.5% vs. 3.0%), which are known toxicities associated with trastuzumab emtansine.

A similar percentage of patients reported AEs that led to discontinuation of trastuzumab emtansine in both treatment arms (13.2% in the trastuzumab emtansine plus placebo arm and 15.2% in the trastuzumab emtansine plus atezolizumab arm). The most common AEs that led to discontinuation of trastuzumab emtansine were thrombocytopenia (1.5% in the trastuzumab emtansine plus placebo arm vs. 5.3% in the trastuzumab emtansine plus atezolizumab arm), AST increase (2.9% vs. 1.5%), ALT increase (2.9% vs. 0.8%), and pneumonitis (1.5% vs. 3.8%). A higher proportion of patients discontinued atezolizumab vs placebo due to an AE (25.8% vs 14.7%, respectively). More frequently, AEs were managed with interruption of atezolizumab or reduction/interruption of trastuzumab emtansine in the combination arm.

One death due to an AE was reported: a case of histiocytosis hematophagic (hemophagocytic syndrome) in a patient treated with trastuzumab emtansine plus atezolizumab that was judged to be study treatment related.

At the final analysis (CCOD: 11 December 2018; Emens et al. 2019b), the incidence of AEs was comparable between the two arms, however the overall incidence of Grade ≥3 AEs was higher in the combination arm: 45% with trastuzumab emtansine plus placebo and 53% with trastuzumab emtansine plus atezolizumab. In particular, the incidence of Grade ≥3 thrombocytopenia, AST elevation, and anemia were numerically increased in

the combination arm. A higher incidence of SAEs, AEs leading to atezolizumab discontinuation, and AEs leading to dose reduction of trastuzumab emtansine were reported in the combination arm. Two patients had died due to AEs in the combination arm (hemophagocytic syndrome and brain hemorrhage due to fall [judged unrelated]) and one patient in the placebo arm (cardiac failure judged to be related to trastuzumab emtansine). Notably, the final analysis was conducted after the study was unblinded with respect to treatment assignment as per the iDMC recommendation (see above) and both investigators and the patients in study were informed accordingly.

Of the trastuzumab emtansine selected AEs, the incidence of thrombocytopenia, hepatotoxicity, peripheral neuropathy and infusion related reaction / hypersensitivity Type 1 were also numerically increased in the combination arm. Among atezolizumab AEs of special interest (AESI), the incidence of immune-mediated rash, immune-mediated hypothyroidism, and immune-mediated pancreatitis toxicity were numerically increased in the combination arm compared with the placebo arm.

Overall, the safety profile of trastuzumab emtansine and atezolizumab in the ITT population was consistent with what is already known about the individual drugs.

1.3.2.1 Preplanned Subgroup Analysis of Patients with PD-L1-Positive Tumors

At baseline, approximately 40% of patients in Study WO30085 (KATE2) were positive for PD-L1 expression by IHC (57 [43%] for trastuzumab emtansine plus atezolizumab and 27 [39%] for trastuzumab emtansine plus placebo). PD-L1-positive disease was defined as tumor-infiltrating immune cells (IC) covering ≥ 1% of tumor area by IHC using the investigational VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody [PD-L1 (SP142) assay].

A pre-planned subgroup analysis according to baseline tumor PD-L1 expression status (CCOD: 11 December 2017) suggested a potential benefit of trastuzumab emtansine plus atezolizumab in the PD-L1-positive subgroup, with a median PFS of 8.5 months with combination therapy vs 4.1 months in the placebo arm (stratified HR = 0.60, 95% CI: 0.32, 1.11, p = 0.099) (Emens et al. 2019a). The ORR was also numerically higher in the PD-L1-positive subgroup with combination therapy (54%) compared with the placebo arm (33%).

At the final analysis (CCOD: 11 December 2018), the OS data suggested a survival advantage with the combination treatment in the PD-L1-positive subgroup compared with the placebo arm. One-year OS was numerically higher with combination therapy (94.3%) compared with placebo (87.9%; stratified HR = 0.55 [95% CI: 0.22, 1.38]). Median OS was not reached in either arm (Emens et al. 2019b).

While the magnitude of benefit in the PD-L1-positive subgroup is uncertain, given the small sample size, wide confidence intervals of the HRs, and imbalances of baseline

prognostic factors between the treatment arms (ECOG PS 0, lower HER2 expression, and PIK3CA mutation) that might have favored the combination arm, the data do indicate that further investigation of trastuzumab emtansine plus atezolizumab is warranted in patients with HER2-positive and PD-L1-positive MBC.

1.3.3 Study WO29522 (IMpassion130)

Study WO29522 (IMpassion130) is an ongoing Phase III multicenter, randomized, placebo-controlled study of atezolizumab in combination with nab-paclitaxel (protein-bound paclitaxel) compared to placebo with nab-paclitaxel for patients with previously untreated metastatic triple-negative breast cancer. A total of 902 patients were enrolled and randomized to either atezolizumab (840mg IV, q2w) or placebo in combination with nab-paclitaxel (100 mg/m^2, q2w) on a 3 week on/1 week off schedule. The co-primary endpoints of the study are PFS by independent review and OS.

At the first interim analysis (the primary [and definitive] analysis for PFS and first interim analysis for OS; median follow-up 12.9 months), treatment with atezolizumab plus nab-paclitaxel compared to placebo plus nab-paclitaxel resulted in a statistically significant reduction in the risk of disease worsening or death in the intent-to-treat (ITT) population (median PFS 7.2 vs. 5.5 months, respectively; HR = 0.80; 95% CI: 0.69, 0.92; p=0.002) (Schmid et al. 2018). In the PD-L1-positive population, median PFS was 7.5 vs. 5.0 months, respectively; HR = 0.62, 95% CI: 0.49, 0.78; p < 0.001. There was a trend for prolonged OS in the ITT population (median OS 21.3 months and 17.6 months, respectively (HR for death = 0.84; 95% CI: 0.69, 1.02; p = 0.08) with a clinically meaningful 9.5-month OS improvement in the PD-L1-positive subpopulation (median OS 25.0 vs 15.5 months, respectively; HR = 0.62, 95% CI: 0.45, 0.86). Due to the hierarchical statistical design, OS results were not formally tested in the PD-L1-positive subpopulation.

At the preplanned second OS interim analysis (data cutoff 2 January, 2019, median follow-up 18 months), the co-primary endpoint of OS was again not significant in the ITT population as the pre-specified boundary (HR ≤ 0.818, available α = 0.021) was not crossed (stratified HR = 0.86, 95% CI: 0.72, 1.02; p = 0.078). In the exploratory OS analysis in patients with PD-L1 immune cell-positive tumors, median OS was 25.0 months with atezolizumab versus 18.0 months with placebo (stratified HR = 0.71, 0.54, 0.94]; not formally tested) (Schmid et al. 2020). An improvement in investigator-assessed PFS was demonstrated with atezolizumab plus nab-paclitaxel relative to placebo plus nab-paclitaxel in both the ITT population (stratified HR = 0.80; 95% CI: 0.69, 0.92; p = 0.0021) and the PD-L1-positive population (stratified HR = 0.63, 95% CI: 0.50, 0.80; p < 0.0001). Results were similar at the final OS analysis (data cutoff 14 April, 2020, median follow-up 18.8 months; Emens et al. 2020). OS was not significant in the ITT population as the prespecified boundary (HR ≤ 0.853, available α = 0.041) was not crossed (stratified HR = 0.87, 95% CI: 0.75, 1.02, p = 0.0770). In the exploratory OS analysis in patients with PD-L1 immune cell-positive tumors, median OS was 25.4

months with atezolizumab versus 17.9 months with placebo (stratified HR = 0.67, 95% CI: 0.53, 0.86; not formally tested).

Overall, the combination of atezolizumab plus nab-paclitaxel had a tolerable safety profile. As of an updated data cutoff of 3 September 2018 (median 15.6 months follow-up), aggregate safety data were available for 890 patients. Grade 3–4 AEs were reported in 49% of the atezolizumab plus nab-paclitaxel group and in 43% of the placebo plus nab-paclitaxel group. The only Grade 3–4 AEs occurring in > 5% of patients were neutropenia (reported in 8.2% of patients in each group), and peripheral neuropathy (reported in 5.5% of patients in the atezolizumab plus nab-paclitaxel group compared to 2.7% of patients in the placebo plus nab-paclitaxel group). Serious AEs (SAEs) occurred in 23% and 18% of patients in the two groups, respectively. The only between-group differences in any-Grade AESI frequencies were for rash (34% vs 26%, respectively), hypothyroidism (17% vs 4%, respectively), hyperthyroidism (4% vs 1%, respectively), and pneumonitis (3% vs < 1%, respectively).

Refer to the most recent version of the Atezolizumab Investigator's Brochure for updated details on studies described above and clinical activity and safety in all patients, regardless of tumor type.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Trastuzumab emtansine is an active regimen in HER2-positive MBC (see Section 1.2). In addition to its cytotoxic activity, trastuzumab emtansine targets intratumoral dendritic cells to potentiate antitumor immunity (Müller et al. 2015). Therefore, combining trastuzumab emtansine with atezolizumab, an anti-PD-L1 antibody that restores antitumor immunity, may result in greater clinical activity than with either drug alone.

Preclinical models provide support for this hypothesis. It has been demonstrated that the addition of PD-1:PD-L1 blockade improves the therapeutic activity of a trastuzumab in a murine experimental model of HER2-positive breast cancer (Stagg et al. 2011; data on file). These findings suggest that anti-PD-L1 immunostimulatory approaches may further capitalize on the immune-mediated effects of therapeutic antibodies. With the potential for therapeutic synergy, combining atezolizumab (anti-PD-L1 antibody) with HER2-targetting antibodies such as trastuzumab emtansine may further enhance the anti-tumor efficacy of these established anti-HER2 treatments.

Cancer immunotherapy is a relatively new focus for breast cancer studies. It is hypothesized that an important mechanism of action of therapeutic antibodies such as trastuzumab emtansine, trastuzumab, and pertuzumab (all humanized monoclonal IgG antibodies) is to induce cellular immunity via interactions with the Fc fragment of the molecule and/or destroy malignant cells, resulting in release of tumor antigens for uptake by antigen-presenting cells, which in turn upregulate immune effector cells. With these mechanisms of action, the combination of trastuzumab emtansine with an anti-PD-L1 inhibitor such as atezolizumab might further enhance anti-tumor immune responses,

thereby improving clinical outcomes for patients with minimal increases in clinically significant toxicities.

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1 (CD80). PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell cancer, hepatocellular cancer, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

While Study WO30085 failed to demonstrate that combining trastuzumab emtansine with atezolizumab would improve outcomes compared with trastuzumab emtansine plus placebo in the overall population, it did indicate a potential benefit of the combination in the pre-planned analysis of the subgroup of PD-L1-positive patients (see Section 1.3.2.1) in metastatic HER2-positve breast cancer. Similarly, Study WO29522 indicated that the combination of atezolizumab with nab-paclitaxel was beneficial in the subgroup of patients with PD-L1-positive tumors (see Section 1.3.3) in the TNBC subtype.

Study MO42319 will employ a similar study design to that used in Study WO30085; however, all patients enrolled to Study MO42319 will have HER2-positive and PD-L1-positive tumors at baseline, building on the proof-of-concept results in the PD-L1-positive subgroup in Study MO42319.

The safety of trastuzumab emtansine is well established and has been evaluated as single-agent in 1871 patients with MBC in clinical studies. The most common AEs for single-agent trastuzumab emtansine (AEs in $\geq$25% of patients) were nausea, fatigue and headache (see Trastuzumab emtansine Investigator's Brochure for detailed safety results). Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis,

pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

Study WO30085 demonstrated that the safety profile of trastuzumab emtansine in combination with atezolizumab was consistent with what is already known about the individual drugs (see Section 1.3.2). To date, no new safety signals have been observed with the combination of trastuzumab emtansine plus atezolizumab in Studies WO30085 and G029831.

Several measures will be taken to ensure the safety of patients participating in this study. Stringent eligibility criteria (Section 4.1) have been designed to exclude patients at higher risk for toxicities from study participation. Administration of trastuzumab emtansine and atezolizumab/placebo will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Close safety monitoring (Section 5.3) rules for dose modifications (Section 5.1.4.1) will be implemented. Patients will undergo periodic safety monitoring by an independent data monitoring committee (iDMC) during the study (Section 3.3.1), including assessment of the nature, frequency, and severity of AEs; details of this safety monitoring will be specified in the iDMC Charter. Furthermore, guidance on management of potential trastuzumab emtansine toxicities (Appendix 18), atezolizumab toxicities (Appendix 19) and potential overlapping toxicities (Appendix 20) is provided.

In the setting of the coronavirus disease 2019 *(*COVID-19*)* pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD 1/PD L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (IFNγ*;* Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient

develops acute SARS CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

While it is not known there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops SARS-Co-2 infection while receiving trastuzumab emtansine.

Pulmonary toxicity has been observed in patients treated with atezolizumab and/or trastuzumab emtansine. Symptoms of interstitial lung disease and pneumonitis may overlap with manifestations of COVID-19 infection and should be carefully evaluated in the diagnostic process. In this study, atezolizumab *is discontinued for all grades of interstitial lung disease and pneumonitis,* and trastuzumab emtansine *is* discontinued for *Grade 3 – 4 adverse events* of interstitial lung disease and pneumonitis.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the NCCN COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021b). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID19 outbreak in a given- area or region.

A risk assessment was also performed by the team on the possible interaction between trastuzumab emtansine and COVID-19 vaccination. The outcome was that a COVID-19 vaccine given to a trial participant has no anticipated drug-vaccine interaction and does not require advice on timing of the vaccination or the implementation of any other risk mitigation activities.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

This trial will enroll patients with HER2-positive and PD-L1-positive LABC or MBC, who have progressed 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. Given the relatively poor prognosis, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for trastuzumab emtansine in combination with atezolizumab is expected to be acceptable in this setting.

2. 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 HER2-positive and PD-L1-positive LABC or MBC. Patients must have progressed 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.

In this protocol, "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).

2.1 EFFICACY OBJECTIVES

2.1.1 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.

- 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
- 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 (a) 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.

2.1.2 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:

- 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
- 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
- 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/QoL as measured by the scales of the 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.

2.1.3 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 the corresponding analysis will no longer be performed.

2.2 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 AEs, 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.

2.3 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.

2.4 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 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.

2.5 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 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, 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 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.

2.6 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.

3. STUDY DESIGN

3.1 *PREMATURE TERMINATION 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 in Section 3.2.1 and Appendix 1 .

3.2 *RATIONALE AND IMPLICATIONS OF UNBLINDING ON STUDY DESIGN AND ASSESSMENTS*

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 (Section 4.3.5). 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 PFS based on investigator tumor assessment and OS will no longer be conducted as per the original study *protocol. 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 (a) 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.*

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, as follows:

- *Patients randomized to Arm A (trastuzumab emtansine and atezolizumab-placebo) who are receiving study treatment will no longer receive placebo (see Section 4.3.2.2).*
- *There is no crossover permitted for patients randomized to Arm A to receive atezolizumab in combination with trastuzumab emtansine.*

- *Patients randomized to Arm B (trastuzumab emtansine and atezolizumab) who are receiving study treatment may continue treatment with both study drugs if considered clinically appropriate, after discussion with the investigator. Trastuzumab emtansine can be continued without atezolizumab if this is in the best interest of the patient (Section 4.6.1).*
  - *Until a revised Informed Consent Form is available, clinical notes should clearly document that this discussion took place between the patient and investigator and that the patient's verbal consent was obtained.*
  - *In the event of toxicity leading to trastuzumab emtansine discontinuation, atezolizumab must also be discontinued (Section 4.3.2.1)*

3.2.1 ***Revised Study Assessments***

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 (Section 4.5.5) 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 (IRF) will not be utilized (see Section 4.5.5).

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 no longer be collected.

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

3.3 DESCRIPTION OF THE 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 positive and PD-L1-positive will not be eligible.

The analysis of tumor tissue PD-L1 status and HER2 gene status will be performed by a central laboratory per diagnostic testing protocol no. RD005510 (D158258) using the investigational VENTANA PD-L1 (SP142) Assay (Appendix 7) and VENTANA HER2 Dual ISH DNA Probe Cocktail (Appendix 6) as performance evaluation for these assays as companion diagnostics for the investigational treatment of atezolizumab and trastuzumab emtansine, respectively, in the target patient population (patients with HER2-positive and PD-L1-positive locally advanced or metastatic breast cancer).

Patients may be prescreened for HER2 and PD-L1 status at a central laboratory by participating in a separate prescreening consent. The prescreening test can be performed up to 12 months before randomization from archival tumor tissue. If a patient consents to prescreening for determination of HER2 and PD-L1, these tests would not need to be repeated during the screening period.

Up to two prescreening samples can be sent for analysis (i.e., one sample for prescreening and an additional sample in the case of a prescreen failure). Pre-

screening does not guarantee patient entry into the study as there is a chance that study enrollment could be completed during the 12-month patient prescreen period.

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.*

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 (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 who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. The investigator will maintain a record of reasons for screen failures (see Section 4.5.1).

Patients must have measurable disease at baseline that is evaluable per RECIST v1.1 (Appendix 4). 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), see Appendix 1 , 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 (see). *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 (Appendix 4) 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 IRF will not be utilized (Section 4.5.5).*

Safety assessments will include the incidence, nature, and severity of AEs and laboratory abnormalities graded per NCI CTCAE v5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

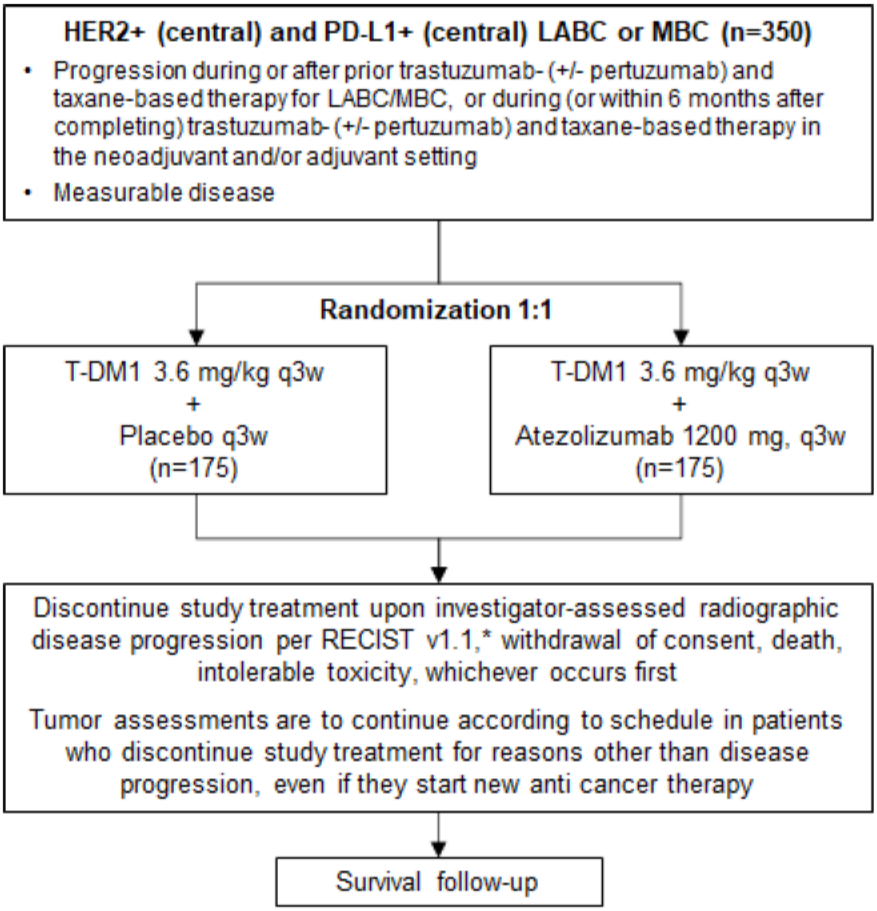
Serum samples will be collected to monitor pharmacokinetics and to detect presence of antibodies to trastuzumab emtansine and atezolizumab. Tumor tissues, plasma, and whole blood samples, will be collected for exploratory biomarker assessments (Appendix 2). *Following the Sponsor's decision to prematurely 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.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 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.

* 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.

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).

3.3.1 Independent Data Monitoring Committee

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 enrollment of the first patient. The summaries and analyses of safety data for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC). The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

After reviewing the data, the iDMC will provide recommendations to the Sponsor as to whether the study should continue, be amended, or stopped, on the basis of the risk–benefit balance to the patient. The Sponsor's Data Review Board (a group consisting of employees of the Sponsor empowered to make critical decisions) will make a decision on the basis of the iDMC's recommendations. Final decisions will rest with the Sponsor.

Any outcomes of these safety 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 as outlined in Section 3.2.

3.4 END OF STUDY AND LENGTH 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.

In addition, the Sponsor may decide to terminate the study at any time. *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 options. The treatment solution for each patient may vary, taking into account local regulations and requirements.*

The total length of the study, from screening of the first patient to the end of the study, *was originally* 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.*

3.5 RATIONALE FOR STUDY DESIGN

3.5.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg q3w (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab as either in monotherapy or in combination with other anti-cancer agents, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg q3w. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg q3w (equivalent to an average body weight–based dose of 15 mg/kg q3w) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.5.2 Rationale for Trastuzumab Emtansine Dose and Schedule

The globally approved regimen of trastuzumab emtansine is 3.6 mg/kg q3w as confirmed in Study TDM4370g/BO21977 (Verma et al. 2012), the pivotal Phase III trial comparing trastuzumab emtansine to lapatinib plus capecitabine in patients with HER2-positive MBC who were previously treated with trastuzumab and a taxane. This dose was investigated in combination with atezolizumab in the Phase Ib study GO29831 and Phase II study WO30085, which offer proof of concept for this dose. Overall, the safety profile of trastuzumab emtansine and atezolizumab in these studies was consistent with what is already known about the individual drugs. As described in Section 1.4, several measures will be taken to ensure the safety of patients participating in this study, including guidance on the management of potential toxicities and dose modifications for trastuzumab emtansine.

3.5.3 Rationale for Patient Population

This study will enroll patients with HER2-positive and PD-L1-positive LABC or MBC.

Therapy with trastuzumab emtansine has been demonstrated to improve PFS and OS compared to lapatinib plus capecitabine in a randomized study for patients with HER2-positive MBC who have received prior trastuzumab or taxane (Verma et al. 2012). However, the PFS of 9 months and OS of 30 months for this patient population still represent an unmet medical need. Despite advances in care for patients with HER2-positive MBC, it remains an incurable disease. Nearly all patients with HER2-positive MBC will eventually suffer disease progression and die from their disease. There is thus still a pressing need for more efficacious therapies with improved safety profiles in patients with HER2-positive disease.

Atezolizumab showed promising anti-tumor activity, as determined by RECIST v1.1 response, across multiple advanced tumor types, including MBC. Inhibition of PD-1/PD-L1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 correlates with response to therapy in several tumor types

(Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016; Spigel et al. 2018).

In the Phase II Study WO30085, the subgroup of patients with LABC or MBC whose tumors expressed PD-L1 (IC 1/2/3) had improved PFS and a trend towards improved OS when treated with trastuzumab emtansine plus atezolizumab compared with trastuzumab emtansine plus placebo (see Section 1.3.2). These data provide a rationale for evaluating the efficacy and safety of adding atezolizumab to trastuzumab in a population of patients with LABC or MBC with HER2-positive and PD-L1-positive tumors.

3.5.4 Rationale for Control Group

Based on the results the EMILIA study (TDM4370g/BO21977; Section 1.2.1; Verma et al. 2012), trastuzumab emtansine was established as the standard of care in patients with HER2-positive MBC who have been previously exposed to trastuzumab and or taxane; the patient population being studied in the current trial (NCCN 2021a; Gennari et al. 2021).

The control arm will be used to ascertain the individual contribution of atezolizumab to efficacy with trastuzumab emtansine in patients with HER2-positive and PD-L1-positive breast cancer. Patients who are randomized to the control group will not be deprived of active therapy because all patients, regardless of treatment assignment, will receive an active, standard-of-care anti-HER2 treatment (i.e., trastuzumab emtansine).

3.5.5 Rationale for Progression-Free Survival and Overall Survival as Multiple Primary Endpoints

In this study, the multiple primary efficacy endpoints will be investigator-assessed PFS and OS. This study will test the hypothesis that treatment with trastuzumab emtansine plus atezolizumab will prolong PFS and OS compared with treatment with trastuzumab emtansine plus placebo.

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Meta-analyses have indicated that PFS can be considered a good measure of clinical benefit for patients with advanced breast cancer (Li and Pan 2018; Adunlin et al. 2015). Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit-risk profile of the new treatment compared with available therapies (FDA 2007; European Medicines Agency 2012).

Multiple indicators support the integrity of Investigator-determined radiographic assessments and, therefore, this study is designed to use INV-PFS as primary endpoint. Appendix 1 to the EMA Guideline on the Evaluation of Anticancer Medicinal Products in Man (2013) states: “Investigator bias is generally not an issue in properly double-blinded

randomized studies" (EMA 2013; possible caveats specific to anti-cancer therapy studies follow this statement). However, there could be a risk of discordance between assessments performed by independent central review committee and investigator assessments in some adjuvant cancers or where cancer immunotherapies are being used (Stone et al, 2019).

Responses will be assessed by a blinded independent central review committee and further sensitivity analyses will be conducted.

Improvement in OS is generally accepted as the best objective measure of clinical benefit for patients with MBC. Recent data also suggest that OS may be a sensitive endpoint for cancer immunotherapy. For example, in a randomized Phase II study (GO28753), patients with advanced NSCLC in the ITT population had a significant improvement in OS when treated with atezolizumab compared with docetaxel, with a stratified HR of 0.73 (95% CI: 0.53, 0.99). PFS in the ITT population was similar in the two treatment arms: HR of 0.94 (95% CI: 0.72, 1.23) (Fehrenbacher et al. 2016).

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 51.7 months in the experimental arm, corresponding to a target OS hazard ratio of 0.60. The median PFS estimated for the control arm (7 months) is based on the PFS observed in Study WO30085 in the subgroup of patients with prior trastuzumab and pertuzumab treatment who were randomized to treatment with trastuzumab emtansine plus placebo.

3.5.6 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti–PD-L1 therapy in the metastatic setting (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016; Spigel et al. 2018; Schmid et al. 2018). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. As previously described (Section 1.3.2.1), an exploratory analysis in Study WO30085 (KATE2) suggested a possible PFS benefit with atezolizumab in combination with trastuzumab emtansine vs trastuzumab emtansine and placebo in the PD-L1–positive subgroup, which was not observed in the PD-L1-negative subgroup. However, the magnitude of the potential benefit is uncertain due to the small sample size and imbalances in baseline factors (Emens et al. 2019a). Interestingly, the predictive nature of PD-L1 expression was also observed in metastatic TNBC. In Study WO29522 (IMpassion130), patients with first line metastatic TNBC treated with atezolizumab plus nab-paclitaxel experienced a prolonged PFS and OS compared with patients treated with placebo plus nab-paclitaxel in the PD-L1-positive but not in the PD-L1-negative subgroup (Schmid et al. 2018). The same result was demonstrated by the Keynote-355 study in patients with

locally recurrent, inoperable or metastatic TNBC treated with pembrolizumab vs placebo in combination with chemotherapy (Cortes et al. 2020). Therefore, only patients with tumor PD-L1 expression defined by expression on tumor-infiltrating immune cells (IC) covering ≥ 1% of tumor area by the PD-L1 SP142 assay will be enrolled in the study. The relationship between PD-L1 expression level measured by various IHC assays and clinical outcomes may be assessed in a retrospective manner.

In addition, other exploratory biomarkers, such as potential predictive and prognostic markers that are related to PD-L1 activity, tumor immunobiology (e.g. CD8, TILs), mechanisms of resistance or tumor type may also be analyzed if supported by either nonclinical or clinical data. KATE2 showed that immune-related biomarker data, such as CD8 IHC expression, and TILs were consistent with the subgroup data in the PD-L1–positive subgroup, showing a treatment benefit with atezolizumab in tumors with high immune biomarkers expression compared to those with low expression. These results support that benefit from atezolizumab-plus-trastuzumab emtansine regimen is likely dependent on pre-existing immunity (Emens et al. 2019a).

Activating PIK3CA mutations in tumors have been evaluated as a resistance marker for HER2-targeted therapies in prior trials. In metastatic HER2−positive breast cancer, (Study WO20698/TOC4129g) worse PFS was observed in patients with PIK3CA mutations (Baselga et al. 2014) while treatment effect was maintained. Study TDM4370g/BO21977 (Verma et al. 2012) showed that no difference in PFS and OS was seen in patients with and without an activating PIK3CA mutation in their tumor when treated with trastuzumab emtansine (Baselga et al. 2016). In the current study, PIK3CA mutations may be measured in baseline tumor tissue to confirm the finding from Study TDM4370g/BO21977.

Müller et al. (2015) demonstrated that trastuzumab emtansine increases tumor infiltrating lymphocytes (TILs) in human primary breast cancer and induces infiltration by effector T cells in murine breast tumors. Additionally, they showed that combining trastuzumab emtansine treatment with blockade of the PD-1/CTLA-4 inhibitory pathway resulted in complete cures in murine models and greatly enhanced T cell responses. Chen et al. (2014) showed in a study in patients with HER2-positive EBC ($n = 22$) that trastuzumab in combination with granulocyte–macrophage colony-stimulating factor/HER2 vaccine triggered a HER2-specific T-cell response. The presence of HER2-specific CD8 T cells in peripheral blood increased over the course of the multiple trastuzumab/vaccination treatment. An exploratory endpoint of this study is to test whether the combination of atezolizumab with trastuzumab emtansine changes expression levels of biomarkers or biomarker panels in the peripheral blood and/or in the tumor compared to those receiving trastuzumab emtansine alone.

Pre-treatment tumor samples and biopsies collected at the time of progression (if clinically feasible) will assist in the study of pharmacodynamic changes related to the activity of trastuzumab emtansine with and without combination treatment with

atezolizumab (changes in infiltration of CD8-positive T cells and other exploratory biomarkers). Peripheral blood samples will also be collected prior to treatment and throughout the course of treatment to evaluate biomarkers (e.g. ctDNA).

In addition, potential correlations of pharmacodynamic markers with the dose, safety, and anti-tumor activity of combination treatment with atezolizumab plus trastuzumab emtansine will be explored.

Tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with acquired resistance to study treatment, are associated with susceptibility to developing AEs, can lead to improved AE monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop AEs. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

3.5.7 Rationale for Immunogenicity Assessments

Immunogenicity assessments will be used to determine whether patients develop ADAs against trastuzumab emtansine and/or atezolizumab, and assess whether the presence of ADAs impact safety, efficacy, or PK (as data allow). Refer to the schedule of activities (Appendix 1) and the schedule of PK, immunogenicity, and biomarker samples (Appendix 2) for details regarding the timing and frequency of blood sample collection to assess ADAs.

A three-tiered analytical testing approach will be used to detect, confirm, and characterize the ADAs against trastuzumab emtansine and atezolizumab. First, screening for the potential emergence of ADAs using bridging immunoassays. Second, confirming the specificity of the response in all screen positive samples through competition with the therapeutic protein in confirmatory immunoassays. Third, characterization of the response in all confirm positive samples in a titration immunoassay (a titer is the $\log_{10}$ of the reciprocal of the sample dilution factor at the cut point used to define positivity). All immunogenicity samples will be analyzed at central bioanalytical laboratories.

3.5.8 Rationale for Non-Standard Clinical Outcome Assessments

Cancer treatments, particularly combination therapies, can produce significant symptomatic AEs. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting AE information directly from patients can provide a better understanding of treatment characteristics and their effects. In order to evaluate the tolerability of trastuzumab emtansine in combination with atezolizumab, patients will be asked to report on their experience related to study treatment-related symptoms selected from the validated PRO-CTCAE item bank (see Section 4.5.9 and Appendix 13 for further details). These symptoms were identified as being salient to patients' experience with trastuzumab emtansine and atezolizumab on the basis of the AEs anticipated for these drugs.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll patients with HER2-positive and PD-L1-positive LABC or MBC who have received prior trastuzumab- (+/- pertuzumab) and taxane-based therapy that is incurable, unresectable, and previously treated with multimodality therapy. Patients must comply with the following inclusion and exclusion criteria.

4.1.1 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 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. Refer to Section 4.5.7 for additional information on tumor specimens collected at screening.

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 $\geq$ 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) $\leq$ 2.5 x upper limit of normal (ULN), with the following exceptions:

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

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

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

4.1.2 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 (see Appendix 15 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid replacement hormone are eligible for the study.
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    - Rash must cover < 10% of body surface area.
    - 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 $\geq$ 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.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

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).

Patients 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. Randomization will be stratified according to the following criteria:

- 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).

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper

interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. Trastuzumab emtansine, total trastuzumab, and DM1 PK and trastuzumab emtansine ADAs will be analyzed for all patients. PK samples collected from patients assigned to the comparator arm will not be analyzed for atezolizumab levels, except by request (e.g., to evaluate a possible error in dosing). Immunogenicity samples from patients assigned to the comparator arm will not be analyzed for atezolizumab ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of an SAE for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, investigators are encouraged to consult with the Medical Monitor prior to performing unblinding.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding is permitted for medical management of immune mediated toxicity and to guide initiation of steroids and other immunosuppressives. When the unblinding is requested, the date and reason for unblinding must be fully documented in source documents and recorded in the case report forms. If unblinding occurs, the site staff should make every effort to ensure that the treatment arm in which the unblinded patient was assigned is not communicated to any Sponsor personnel or designee involved in the study. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to an investigational medicinal product (IMP; defined in Section 4.3). The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

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 (Section 4.3.5). 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 PFS based on investigator tumor assessment and OS will no longer be conducted as per the original study *protocol. 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 (a) 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.*

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.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are trastuzumab emtansine, atezolizumab, and placebo.

There are no non-investigational medicinal products (NIMPs) in this study.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Trastuzumab Emtansine

Trastuzumab emtansine will be supplied by the Sponsor as a vial containing 160 mg powder for concentrate for solution for infusion. After reconstitution one vial of 8 mL solution contains 20 mg/mL of trastuzumab emtansine. For information on the trastuzumab emtansine formulation, see the pharmacy manual and the Trastuzumab emtansine Investigator's Brochure.

4.3.1.2 Atezolizumab and Placebo

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

Placebo will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial, equivalent to atezolizumab but without the active agent.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.3.

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

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated AEs, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification (allowed for trastuzumab emtansine only) and treatment interruption or discontinuation for patients who experience AEs are provided in Section 5.1.4 and Appendix 18 (trastuzumab emtansine), Appendix 19 (atezolizumab), and Appendix 20 (potential overlapping toxicities).

4.3.2.1 Trastuzumab Emtansine

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 $\geq$ 10% compared to the previous visit or baseline. Administration may be delayed to assess or treat AEs. Dose reduction of trastuzumab emtansine will be allowed, following the dose reduction levels provided in Table 5. Once a dose has been reduced for AE(s), it must not be re-escalated.
If trastuzumab emtansine is discontinued because of toxicity, it should not be re-administered. If trastuzumab emtansine is discontinued for any reason, atezolizumab/placebo should also be discontinued.

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.

Refer to Table 2 for guidelines on administration of first and subsequent infusions of trastuzumab emtansine.

Table 2 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs as indicated in Appendix 1 • Administer the initial dose as a 90-minute (±10 min) intravenous infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Record patient's vital signs as indicated in Appendix 1 • If the patient experienced an IRR with any previous infusion, premedication for nausea and infusion reactions (e.g., analgesics, etc.) may be administered at the investigator's discretion. • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute (± 10 min) infusions • Patient should be observed during the infusions and for at least 30 minutes after infusion.

IRR = infusion related reaction.

4.3.2.2 Atezolizumab and Placebo

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity (see Section 3.3 for details).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 17 . Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an IRR with any previous infusion, premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for subsequent doses, as clinically indicated. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR, or 60 (±15) minutes if the patient experienced an IRR with the previous infusion. • If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

IRR = infusion related reaction.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 19 .

No dose modification for atezolizumab is allowed. If atezolizumab/placebo is discontinued for toxicity, treatment with trastuzumab emtansine may continue, if clinically indicated.

4.3.3 Sequence of Study Drug Administration

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

Guidelines for treatment interruption or discontinuation and the management of specific AEs are provided in Section 5.1.4 and Appendix 18 (trastuzumab emtansine), Appendix 19 (atezolizumab), and Appendix 20 (potential overlapping toxicities).

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration of atezolizumab/placebo.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the applicable Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Trastuzumab Emtansine and Atezolizumab

The Sponsor will offer continued access to Roche IMPs (trastuzumab emtansine and atezolizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (trastuzumab emtansine and atezolizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs (trastuzumab emtansine and atezolizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for breast cancer.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for breast cancer.
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

*Following the Sponsor's decision to terminate the study, pa*tients may be eligible to receive trastuzumab emtansine or trastuzumab emtansine in combination with atezolizumab as part of an extension study *(BO25430) or as part of a Post-Trial Access Program or other local option. The treatment solution for each patient and country may vary, taking into account local regulations and requirements.*

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.

Patients must be instructed not to take any concomitant medications (over-the-counter or other products) during the study without prior consultation with the investigator.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)

  Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.
- Inactivated vaccinations such as influenza, COVID-19
- Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for prevention of skeletal related events
- Palliative radiotherapy to treat pre-existing bone metastases only

Premedication with antihistamines, anti-pyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, as clinically indicated.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 17).

4.4.2 Cautionary Therapy

4.4.2.1 Corticosteroids, Immunosuppresive Medications and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered as clinically indicated.

Systemic corticosteroids or immunosuppressive medications are recommended, as clinically indicated, for the treatment of specific AEs when associated with atezolizumab therapy (refer to Appendix 19 for details).

Corticosteroids may also be used for the treatment of isolated brain metastases according to local standard of care. Corticosteroids should be tapered to a stable total daily dose equivalent to ≤2 mg of dexamethasone before the patient receives the next cycle of treatment.

4.4.2.2 Medications Given with Precaution due to Effects Related to CYP Enzymes

In vitro data suggest that DM1, a component of trastuzumab emtansine is metabolized mainly by cytochrome p450 (CYP) CYP3A4 and, to a lesser extent, by CYP3A5, and there is a moderate to high potential for drug-drug interaction with any medication that is metabolized by or strongly inhibits or induces these enzymes. DM1 does not induce or inhibit P450-mediated metabolism in vitro. Therefore, the medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be assessed by the investigator prior to concomitant administration with trastuzumab emtansine. The Medical Monitor is available to advise as needed.

- Strong CYP3A4/CYP3A5 inhibitors, including, but not limited to, ketoconazole and itraconazole

The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above. If a strong CYP3A4/5 inhibitor needs to be co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions.

4.4.2.3 Herbal Therapies

Any traditional Chinese medication/Herbal remedies with approval for use as anti-cancer treatment (regardless of the type of cancer) will not be permitted. Traditional Chinese medication/Herbal remedies for indications other than anti-cancer treatment, such as supportive care, are discouraged but are permitted at the discretion of the investigator and must be reported on the appropriate eCRF.

4.4.2.4 Therapies Given for Chemotherapy Induced Thrombocytopenia

Concomitant use of therapies for prevention and treatment of thrombocytopenia induced by chemotherapy, e.g. thrombopoietin receptor agonists, recombinant thrombopoietins, recombinant interleukin, should be avoided. Adherence to the relevant safety management guidelines to institute appropriate dose modifications of trastuzumab emtansine in case of thrombocytopenia is recommended (Appendix 18). If any of those agents needs to be co-administered with trastuzumab emtansine in line with local standard clinical practice, patients should be closely monitored for adverse reactions and overlapping toxicities.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, for various time periods prior to starting study treatment, depending on the agent (Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment
- Investigational therapy within 21 days prior to initiation of study treatment and during study treatment
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of study treatment
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab
- RANKL inhibitor (denosumab): Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study.
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRI scans of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed

4.4.4 Prohibited Food

Consumption of grapefruit or grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the final dose of study treatment.

4.4.5 Additional Restrictions

Excessive alcohol intake should be avoided (occasional to moderate use is permitted).

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 . All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from the patient or a legally-authorized representative before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Prior to signing the main Informed Consent Form for the study, patients may consent to the collection of archival tumor tissue for determination of HER2 and PD-L1 expression at a central laboratory to determine eligibility by signing a Prescreening Informed Consent Form. The test results must be obtained 12 months prior to randomization. If a patient consents to prescreening for determination of HER2 and PD-L1, these tests would not need to be repeated during the screening period.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened, to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including hormone receptor status, prior cancer therapies, and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Cycle 1, Day 1 visit will be recorded.

Hormone receptor status will be determined in the local laboratory according to guidelines from the American Society of Clinical Oncology/College of American Pathologists (Allison et al. 2020).

At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Breast cancer history includes prior cancer therapies and procedures.

Demographic data will include age, sex, and self-reported race or ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs are to be measured before, during, and after *each* infusion as outlined in Table 4, and at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Table 4 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab/ placebo	• Within 60 minutes prior to the atezolizumab infusion • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.	• Within 60 minutes prior to the atezolizumab infusion • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.
Trastuzumab emtansine	• Vital signs must be assessed before and after *each* dose administration.	• Vital signs must be assessed before and after *each* dose administration.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline (screening) and then every 6 weeks (± 7 days) following treatment initiation, regardless of dose delays, until investigator-assessed radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor. Thus, tumor assessments are to continue according to schedule in patients who discontinue study treatment for reasons other than disease progression, even if they start new anti-cancer therapy. If clinically indicated, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable (and non-measurable) lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining

informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined below.

Following the announcement of premature study termination, tumor assessments will be conducted as per standard of care and recorded in the eCRF until disease progression or discontinuation of the study.

4.5.5.1 Radiographic Assessments

Screening assessments must include CT scans (with contrast) or MRI scans of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, and pelvis should be performed. A CT scan with contrast or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. See Section 4.1.2 for CNS-related exclusion criteria. A bone scan (or other suitable modality for bone imaging, e.g., NaF or FDG-PET) will also be performed at screening. If clinically indicated, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable (and non-measureable) lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Brain scans (preferably MRI) must be conducted at all subsequent tumor evaluations in patients with known brain metastases. Patients without brain metastases at baseline should have brain scans (preferably MRI) as clinically indicated. A bone scan (or other suitable modality for bone imaging e.g., NaF or FDG-PET) should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

The use of radiopharmaceutical products (e.g., 18F-FDG, Tc-99m, MIBG) and contrast agents (e.g., gadolinium-based or iodinated contrast media) in study imaging assessments will be consistent with standard/local practice, and will not involve a route of administration, dose, patient population, or any other factor that significantly increases the risk (or decreases the acceptability of the risk) to patients. The products employed in these procedures will be at the discretion of participating investigators and shall be locally authorized or otherwise used in compliance with local regulations. The results of

this study (MO42319) will not be used to support any new indication or change in labeling for these products.

4.5.5.2 Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to RECIST v1.1 (Appendix 4). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

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 and an IRF will not be utilized (see Section 4.5.5).*

4.5.6 Left Ventricular Ejection Fraction Assessment

Left Ventricular Ejection Fraction (LVEF) will be assessed by ECHO or MUGA. LVEF will be monitored at baseline, and on Day 15–21 of Cycle 1, and every fourth cycle thereafter. Additional LVEF measurements may be performed as clinically indicated.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation (aPTT and INR)
- Serum or urine pregnancy test for women of childbearing potential, including women who have had a tubal ligation as indicated in Appendix 1 . If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  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 sthe investigator (e.g., Müllerian agenesis). Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being post-menopausal (≥12 months of amenorrhea).

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick permitted
- Thyroid-function test (thyroid-stimulating hormone [TSH], free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free T4)
- HIV serology: (tested prior to patient enrollment in the study)

  HIV-positive patients are excluded from study participation.
- HBV serology (tested prior to patient enrollment in the study): HBsAg, HBsAb, and total HBcAb for all patients; HBV DNA for patients with a negative HBsAg test and a positive total HBcAb test
- HCV serology (tested prior to patient enrollment in the study): HCV antibody for all patients; HCV RNA for patients with a positive HCV antibody test
- C-reactive protein

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Archival or newly collected tumor tissue sample obtained at screening for determination of PDL1 expression and HER2 expression and for exploratory research on biomarkers and biomarker assay development

  A representative 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.

  Tumor tissue should be of good quality as determined on the basis of total and viable tumor content. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. These requirements are requested in order to maximize the chances of receiving valid results which would allow the patient to enter the study.

  Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not acceptable.

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.
- Tumor tissue sample obtained at the time of progression, if deemed clinically feasible and the patient would not be put at risk, for exploratory research on biomarkers and biomarker assay development

A representative FFPE tumor specimen in a paraffin block (preferred) or a minimum of 10 slides containing unstained, freshly cut, serial sections must be submitted, preferably along with an associated pathology report, if available.

Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. In case new line therapy is purely anti-hormonal, biopsy could be taken after it is started.

Samples collected via resection, core-needle biopsy (preferably three cores), or excisional, incisional, punch, or forceps biopsy are preferred.

- Blood and plasma samples for exploratory research on biomarkers at baseline and during treatment and at disease progression. *Following the announcement of premature study termination, these samples will no longer be collected.*
- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti neutrophil cytoplasmic antibody

  The baseline sample will be collected prior to the first dose of study drug on Cycle 1, Day 1. For patients who show evidence of immune-mediated toxicity, additional samples may be collected and will be analyzed centrally.
- PK samples:

  Serum samples will be assayed for atezolizumab, trastuzumab emtansine, and total trastuzumab concentrations using validated immunoassays.

  Plasma samples will be assayed for DM1 concentration using a validated liquid chromatography-tandem mass spectrometry.
- Serum samples for assessment of anti-drug antibodies (ADAs) to atezolizumab and trastuzumab emtansine through use of validated immunoassays
- *Following the announcement of premature study termination, samples for autoantibodies, PK or ADA samples will no longer be collected.*

Instruction manuals and supply kits will be provided for all central laboratory assessments.

Exploratory biomarker research may include, but will not be limited to, analysis of proteins, genes or gene signatures associated with HER2 pathway, tumor immune biology, PD-L1 by various IHC assays, lymphocyte subpopulations (e.g. CD8, TIL), T-cell receptor repertoire, cytokines associated with T-cell activation and ctDNA. Analyses may involve extraction of DNA, ctDNA, or RNA, analysis of mutations, and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will focus on somatic variants. NGS methods may include whole genome sequencing (WGS)/whole exome sequencing (WES), but only at participating sites (see Section 4.5.10).

For China only, collection and submission of blood and plasma samples for biomarker analysis and the number of required slides for the exploratory analyses using tumor tissue samples are contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Tissue samples collected for eligibility testing [pretreatment] and at disease progression as well as whole blood and plasma samples collected for biomarker research (including their derivatives) will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time when the final Clinical Study Report has been completed, whichever occurs first. For patients who are not enrolled, remaining tissue blocks will be returned to the site no later than 2 months after eligibility determination. Slides will not be returned.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Data generated from samples collected for exploratory biomarker research will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

A 12-lead ECG is required at screening and as clinically indicated. Refer to Appendix 1 for the schedule of ECG assessments.

ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.9 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to more fully characterize the clinical profile of atezolizumab. In addition, PRO instruments will enable the capture of each patient's direct experience with atezolizumab.

PRO data will be collected through use of the following instruments: European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaires for cancer (EORTC QLQ-C30) and breast cancer (EORTC QLQ-BR23), NCI (PRO-CTCAE), EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), and the 'Treatment Burden' item from the EORTC IL46 library.

All patients will complete the EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-BR23, and NCI PRO-CTCAE at 3 months after radiographic disease progression per RECIST v1.1.

Following the announcement of premature study termination, PRO assessments will no longer be collected.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered or interviewer-administered (as appropriate) at the clinic or at home at specified timepoints during the study (see schedule of PRO assessments in Appendix 3). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. Laboratory and weight assessments can be completed before the PROs are administered; however, the results of these assessments should not be given to the patient prior to completing the PROs.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor at site, or using the online ePRO completion tool at home (at timepoints specified below only). Instructions for phone administration of PROs will be provided to sites.

The electronic device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint (refer to Appendix 3 for the frequency and timing of PRO assessments in clinic). The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10–15 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

The patient should complete the PRO-CTACE assessments on Day 8 and Day 15 of Cycles 1, 2, and 3 at home using the online ePRO completion tool (see Appendix 3). If the patient does not have access to the online ePRO completion tool at home, and cannot come to the study site to use the electronic device, the site can call the patient and collect the PRO-CTCAE assessments on Day 8 and Day 15 of Cycles 1, 2, and 3 by telephone. The telephone is not to be used to collect PRO data at any other timepoint.

PRO assessments at other timepoints in the treatment period, and the follow-up PRO assessments (3 months after study completion/early discontinuation visit), will be completed at the study site through the use of an electronic device. For the follow-up PRO assessments only, the online ePRO completion tool (but not the telephone option) may be used if the patient cannot attend the study site.

Patients should be given the following instructions for completing the PRO instrument at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.

- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al.1993; Fitzsimmons et al. 1999) (see Appendix 10). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status and quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the global health status and QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent." The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

EORTC QLQ-BR23

The QLQ-BR23 is a modular supplement to the EORTC quality-of-life questionnaire for use in breast cancer (Sprangers et al. 1996; see Appendix 11 . This module consists of 23 additional self-reported items assessing disease or treatment symptoms (systemic therapy side effects, breast symptoms, arm symptoms, and hair loss) and aspects of patient functioning (body image, sexual functioning, and future perspective). One question that is specific to women will not be answered by men. The QLQ-BR23 module takes approximately 5–10 minutes to complete.

EuroQol EQ-5D-5L

The EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 12). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015) (see Appendix 13). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert

scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of nine symptoms deemed most applicable to the current treatments has been selected for this study (fatigue, chills, headache, cough, peripheral neuropathy, rash, aching muscles, aching joints, pain; see Appendix 13). Symptoms have been selected on the basis of the AEs anticipated for trastuzumab emtansine and atezolizumab.

Treatment Burden Item (EORTC IL46)

The treatment burden item from the EORTC item library, “To what extent have you been troubled with side-effects from your treatment?”, will be administered to assess the overall burden of treatment (Appendix 14).

4.5.10 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing AEs, can lead to improved AE monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research may include exploration of germline variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.10) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop AEs. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication. Refer to Section 4.5.7 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition

- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to trastuzumab emtansine and atezolizumab, diseases, or drug safety:

- Leftover blood, plasma, serum, and tumor tissue samples, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop AEs.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her sample(s). If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (trastuzumab emtansine plus atezolizumab/placebo) if any of the following are met:

- Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

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.

- Intolerable toxicity related to study treatment, including development of an immunemediated AE determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy or use of a prohibited therapy (see Section 4.4.3)
- Pregnancy
- Patient withdrawal of consent

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit 28 – 42 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1 and Appendix 3 , respectively).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or the Sponsor terminates the study. Study staff may use a public information source (e.g., county records) to obtain information about survival status only. At 3 months after the treatment completion/discontinuation visit, patients will undergo the PRO assessments described in Appendix 3 .

Following the announcement of premature study termination, data on survival and new anti-cancer therapies will no longer be collected. If patients are already in follow-up, it is recommended that patients in follow-up return to the site for a final visit before being discontinued from the study. If there are unresolved AEs, these should be checked for resolution and any laboratory tests should be performed as necessary or clinically indicated.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor informed all investigators of premature study termination on 15t December 2022.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan has been developed considering the risk measures for each IMP as well as the potential overlapping toxicities. While the safety profile of trastuzumab emtansine is generally well understood given its approval for treatment of HER2-positive LABC and MBC in patients treated previously with trastuzumab and or a taxane, atezolizumab is currently in clinical development and human experience is currently limited, and the entire safety profile of atezolizumab is not known at this time. The safety considerations are based on results from nonclinical and ongoing clinical studies and published data on similar molecules.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria (Section 4.1) have been designed to exclude patients at higher risk for toxicities from study participation. Administration of trastuzumab emtansine and atezolizumab/placebo will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Patients will undergo safety monitoring by an iDMC (Section 9.5) during the study, including assessment of the nature, frequency, and severity of AEs; details of this safety monitoring will be specified in the iDMC Charter.

Guidelines for managing patients who experience anticipated AEs, including criteria for dosage modification (allowed for trastuzumab emtansine only) and treatment interruption or discontinuation, are provided in Section 5.1.4 and Appendix 18 (trastuzumab emtansine), Appendix 19 (atezolizumab), and Appendix 20 (potential overlapping toxicities). Refer to Sections 5.2–5.6 for details on safety reporting (e.g., AEs, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for infections (including SARS-CoV-2) prior to and during study participation should be considered according to local/institutional guidelines or those of applicable professional societies (e.g., ASCO/ESMO).

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome involving the inflammatory cytokines IL-6, IL-10, IL-2 and interferon-gamma (IFNγ) (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of

SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Please refer to the latest versions of the trastuzumab emtansine and atezolizumab Investigator Brochure's for a complete and most up to date summary of safety information.

5.1.1 Risks Associated with Trastuzumab Emtansine

The safety plan for patients in this study is based on the known nonclinical toxicities of trastuzumab emtansine, on clinical experience with trastuzumab emtansine in completed and ongoing studies, and clinical toxicities related to its components (trastuzumab and maytansine-, the parent drug of DM1). The anticipated important safety risks and potential safety risks of trastuzumab emtansine are outlined below and detailed in the Investigator's Brochure. Please refer to the Investigator's Brochure for a complete summary of safety. Guidance to manage such anticipated toxicities is detailed in Appendix 18 and Appendix 20 .

5.1.1.1 Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving trastuzumab emtansine. Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions.

Patients with dyspnea at rest due to complications of advanced malignancy, comorbidities, and receiving concurrent pulmonary radiation therapy may be at risk of pulmonary events.

Patients who have experienced a pulmonary event should be carefully evaluated before commencing trastuzumab emtansine treatment.

Patients diagnosed with *Grade* ≥ 3 ILD or pneumonitis must permanently discontinue treatment with trastuzumab emtansine. *If the patient experiences a Grade 1 event, the dose should be withheld for up to 42 days, to allow resolution to Grade 0. Upon resolution, trastuzumab emtansine can be continued at the same dose level. If not resolved within 42 days, treatment should be discontinued. Dose reductions are recommended for Grade 2 pulmonary events (i.e., pneumonitis, ILD). The dose should be held to allow resolution to Grade 0 prior to resuming trastuzumab emtansine at a lower dose level (Table 5). If not resolved within 42 days, treatment should be discontinued.*

Guidelines for management of trastuzumab emtansine in patients who develop ILD or pneumonitis are provided in Appendix 20.

5.1.1.2 Hepatotoxicity

The following events have been reported with administration of trastuzumab emtansine:

- Serious he.patobiliary disorders

  Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and hepatobiliary disorders with a fatal outcome due to drug-induced liver injury, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases may have been confounded by concomitant medications with known hepatotoxic potential.

- Increased serum transaminases

  Asymptomatic increases in serum transaminase concentration (transaminitis) have been observed. Grade 1 and 2 events have been observed frequently; Grade 3 and 4 events have been observed less commonly. The incidence of increased AST was substantially higher than that for increased ALT. Increases in AST and ALT were commonly observed by Day 8 of each cycle and generally improved or returned to baseline by Day 21. A cumulative effect of trastuzumab emtansine, that is, an increase in the proportion of patients with Grade 1 or 2 elevations in transaminases with successive cycles has been observed; however, there was no increase in the proportion of patients with Grade 3 abnormalities over time.

- NRH

  Cases of NRH have been identified from liver biopsies in patients treated with trastuzumab emtansine who presented with signs and symptoms of portal hypertension. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules. NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can only be confirmed by histopathology. Biopsy-confirmed NRH leading to fatal hepatic failure has been reported.

  NRH should be considered in all patients with clinical symptoms of portal hypertension, even with normal transaminases, and no other manifestations of cirrhosis; in patients with a cirrhosis-like pattern seen on a CT scan of the liver; and/or in patients with liver failure following long-term treatment with trastuzumab emtansine.

Patients must meet specified hepatic laboratory test requirements to be included in this study (Section 4.1).

Hepatic laboratory parameters will be monitored as described in the schedule of assessments (Appendix 1).

Guidelines for management of trastuzumab emtansine in patients who develop increased serum transaminases, increased serum bilirubin, or NRH are provided in Appendix 20.

5.1.1.3 Left Ventricular Dysfunction

Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. To date, significant cardiac events, including LVEF of < 40%, have been observed (infrequently) in clinical trials of trastuzumab emtansine; therefore, symptomatic CHF is a potential risk.

Patients must meet specified LVEF requirements to be included in this study (Section 4.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO) or MUGA scans as described in Section 4.5.6 and the schedule of assessments (Appendix 1).

Guidelines for patient monitoring and management of trastuzumab emtansine in patients who develop left ventricular dysfunction are provided in Appendix 18.

Patients who discontinue study treatment for heart failure or LVEF decline should continue to undergo LVEF assessments according to the schedule of activities (Appendix 1) —irrespective of the initiation of alternative systemic anti-cancer therapy—until resolution, improvement to baseline status, or death. Additional LVEF assessments may be conducted for these patients (beyond those specified in the schedule of activities), according to the investigator's clinical judgment. The results of these assessments should be reported in the eCRF.

5.1.1.4 Infusion-Related Reactions and Hypersensitivity Reactions

Infusion-related reactions (IRRs) and hypersensitivity reactions have been reported with administration of trastuzumab emtansine. Despite the different pathophysiology of IRRs (reactions involving cytokine release) and hypersensitivity (allergic) reactions, the clinical manifestations are the same. In general, IRRs are expected to be more frequent and severe with the first infusion and to decrease in number and severity over time. The severity of true hypersensitivity reactions would be expected to increase with subsequent infusions.

IRRs, characterized by one or more of the following symptoms —flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated.

Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine. Patients with a history of intolerance to trastuzumab will be excluded from this study (Section 4.1).

Administration of study treatment will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical

emergencies. Patients should be closely monitored for IRRs during and after each infusion of study treatment, as described in Section 4.3.2.1.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in Appendix 18.

5.1.1.5 Hematologic Toxicity (Thrombocytopenia)

Thrombocytopenia has been reported in patients enrolled in clinical trials evaluating trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (platelet count $\geq$ 50,000/μL), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (platelet count $\geq$ 75,000/μL) by the next scheduled dose (i.e., within 3 weeks). Evolution of the safety parameter across various clinical studies has shown a higher incidence and severity of thrombocytopenia in Asian patients.

Patients with thrombocytopenia ($\leq$ 100,000/mm^3) and patients on anticoagulant treatment should be monitored closely during treatment with trastuzumab emtansine. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Rare cases of severe prolonged thrombocytopenia ($\geqslant$ Grade 3 thrombocytopenia lasting for more than 90 days) have been reported with trastuzumab emtansine based on cumulative data review. In most of these cases, patients received concomitant recombinant human thrombopoietin (rh-TPO). Trastuzumab emtansine has not been studied in patients with platelet counts $\leq$ 100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater ($<$ 50,000/mm^3), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq$ 75,000/mm^3).

Declines in other hematopoietic lineages, for example, leukopenia, neutropenia, and anemia, were less frequent than that observed for platelets.

Patients must meet specified hematologic laboratory test requirements to be included in this study (Section 4.1).

Hematologic laboratory parameters will be monitored as described in Section 4.5 and the schedule of assessments (Appendix 1). Patients on anticoagulant or antiplatelet treatment should be monitored closely.

Guidelines for management of trastuzumab emtansine in patients who develop hematologic toxicity are provided in Appendix 18 .

5.1.1.6 Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with trastuzumab emtansine. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Caution should be used with these agents, and additional monitoring should be considered when concomitant use with trastuzumab emtansine is medically necessary.

5.1.1.7 Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine.

Patients with Grade ≥ 3 peripheral neuropathy will be excluded from this study (Section 4.1).

Patients will be clinically monitored on an ongoing basis for signs or symptoms of peripheral neuropathy as described in Section 4.5 and the schedule of assessments (Appendix 1).

Guidelines for management of trastuzumab emtansine in patients who develop peripheral neuropathy are provided in Appendix 18.

5.1.1.8 Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and consisted of erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Rare reports of more severe events, such as cellulitis, pain (tenderness and burning sensation), and skin irritation, have been reported as part of the continuing surveillance of trastuzumab emtansine safety. These reactions have been observed more frequently within 24 hours of infusion.

The infusion site will be closely monitored for possible subcutaneous infiltration during drug administration, as described in Section 4.3.2.1. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. Patients should be managed symptomatically per local institutional guidelines.

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated: pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and

lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 19 and Section 6 of the atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.3 Risks Associated with Combination Use of Atezolizumab and Trastuzumab Emtansine

The following AEs are potential overlapping toxicities associated with combination use of atezolizumab and trastuzumab emtansine: suspected hepatotoxicity and pneumonitis.

Suggested workup and management guidelines for overlapping toxicities between atezolizumab and trastuzumab emtansine are provided in Appendix 20 .

5.1.4 Management of Adverse Events

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable as described in the protocol. Dose delays, reductions and management guidelines are designed to ensure patient safety.

Guidelines for management of AEs associated with study treatment are provided in Appendix 18 (trastuzumab emtansine), Appendix 19 (atezolizumab), and Appendix 20 (potential overlapping toxicities).

5.1.4.1 Dose Modification

Dose reductions for atezolizumab are not allowed during this study. Dose reductions for trastuzumab emtansine are allowed as described below.

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.
The severity of AEs will be graded according to the NCI CTCAE v5.0.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be attributable solely to one component of the study treatment (i.e., trastuzumab emtansine, atezolizumab or placebo), then the dose of that component should be delayed or modified in accordance with the guidelines below. If trastuzumab emtansine is held or discontinued for toxicity, then atezolizumab or placebo must also be held or discontinued, respectively.
- When study treatment is temporarily interrupted because of toxicity caused by trastuzumab emtansine or atezolizumab/placebo, the treatment cycles will be restarted such that the atezolizumab/placebo/+trastuzumab emtansine infusions remain synchronized.
- Study treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol

requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

- There will be no dose reduction for atezolizumab or placebo in this study. Patients may temporarily suspend study treatment if they experience toxicity that is considered related to atezolizumab or placebo and requires a dose to be withheld. If atezolizumab/placebo is withheld because of related AEs for >12 weeks after event onset, then the patient will be discontinued from atezolizumab or placebo treatment and will be followed for safety and efficacy as specified in Section 3.3. Treatment with trastuzumab emtansine may continue according to the judgement of the investigator. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab or placebo after a hold >12 weeks, study drug may be restarted. The acceptable length of the extended period of time must be based on the investigator's assessment of benefit-risk and in alignment with the protocol requirements for the duration of treatment, and should be documented by the investigator. The Medical Monitor is available to advise as needed.

  If patients must be tapered off steroids for the treatment of AEs related to atezolizumab or placebo, study treatment may be withheld for >12 weeks until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of the extended period of time must be based on the investigator's assessment of benefit-risk and in alignment with the protocol requirements for the duration of treatment, and should be documented by the investigator. The Medical Monitor is available to advise as needed.

- If significant trastuzumab emtansine-related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for ≤ 42 days after the last dose was received. “Significant” and “related” will be based on the judgment of the investigator. The Medical Monitor is available to advise as needed. For example, alopecia even if considered related to trastuzumab emtansine would most likely not be considered to be significant. Fatigue may or may not be considered either related or significant. In general, when the significant related toxicity (or any other toxicity that the investigator chooses to delay dosing for) resolves to Grade 1 or baseline, the patient may resume trastuzumab emtansine if the delay is not >42 days from the last dose received.

  Patients should be re-evaluated weekly during the delay, whenever possible. If dosing resumes, the patient may receive trastuzumab emtansine either at the same dose level as before or at one lower dose level (Table 5), at the discretion of the investigator. Subsequent cycles should remain q3w, and patients should be assessed for toxicity as described in Appendix 18 to Appendix 20 . If a patient requires a dose reduction, dosing will be reduced by one dose level as per Table 5.

  A maximum of two dose reductions is allowed for trastuzumab emtansine. No dose re-escalation is permitted. A patient treated with 2.4 mg/kg of trastuzumab emtansine who develops an AE requiring a dose reduction must discontinue study treatment and will be followed for safety, disease progression and survival (Appendix 1).

Patients who experience a Grade 3 or 4 hematologic events, other than thrombocytopenia, should be checked at least weekly for recovery. If values do not recover to baseline or Grade ≤1 within 42 days from the last dose received, the patient will be discontinued from study treatment and will be followed for safety, disease progression, and survival (Appendix 1).

Table 5 Dose Modification Scheme for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level (mg/kg, q3w)
Starting dose	3.6
First dose reduction	3.0
Second dose reduction	2.4
Requirement for further dose reduction	Discontinue treatment

Note: The dose of trastuzumab emtansine, once reduced, may not be re-escalated. A maximum of two dose reductions is allowed; patients with any further requirement for dose reduction will discontinue treatment with trastuzumab emtansine.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and AESI, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious AEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Hepatitis, including AST or ALT $>10\times$ ULN
- Transaminitis Grade ≥ 2 (AST or ALT $>3\times$ the ULN and bilirubin $>2\times$ the ULN or AST/ALT $>10\times$ the ULN)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of a study treatment is suspected.
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis (HLH), and macrophage activation syndrome (MAS)
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*
- Systemic lupus erythematosus
- Autoimmune hemolytic anemia
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders
- Vasculitis

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study treatment, all AEs will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and SAEs and AESI will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. Table 6 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the AE suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of study treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to study treatment; and/or the AE abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon rechallenge.
NO	An AE will be considered related, unless it fulfills the criteria specified below. Evidence exists that the AE has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and cytokine release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or “cytokine release syndrome”). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event on the Adverse

Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between these IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 19.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme

severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as AEs.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$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 considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an AESI (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of locally advanced or metastatic breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the AE reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see

Section 5.4.2). An iDMC will monitor the frequency of deaths from all causes, along with other safety data.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the AE reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Locally Advanced or Metastatic Breast Cancer

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of breast cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of breast cancer").

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on both clinical and laboratory findings (physical exam, biopsy, breast imaging, radiologic evidence, etc.). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an AE.
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Hospitalization for a minor condition for which the patient suffers an AE, but does not meet the definition of an overnight admission (e.g., tooth extraction)

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Note: Special situations are not in themselves AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For

trastuzumab emtansine and atezolizumab (or matching placebo), AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

In addition, all special situations associated with trastuzumab emtansine and atezolizumab (or matching placebo), regardless of whether they result in an AE, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO-CTCAE or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (via PRO-CTCAE) with investigator reports of AEs. Sites are not expected to review the PRO-CTCAE or other PRO data for AEs.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For SAEs and AESI, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for all sites

Medical Monitor:	[redacted]
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Emergency Medical Contact:	[redacted] MD
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, SAEs and AESI will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting SAEs that occur after the reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study treatment. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy

Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study treatment. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and

reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an AE.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1), resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For SAEs, AESI, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for SAEs and AESI (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of an SAE that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/ Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and AESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Trastuzumab emtansine	Trastuzumab emtansine Investigator's Brochure
Atezolizumab	Atezolizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The statistical considerations and analysis plan are summarized below. All details of the analyses will be described in the Statistical Analysis Plan (SAP) as part of the Data Analysis Plan. The SAP overrides the analyses described in the statistical section of the protocol, as applicable.

6.1 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 arm 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 as outlined in Section 3.1, 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 only be reported in a descriptive way. No formal testing will be performed and no control for the overall type I error (a) 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment arm comparability will include summaries of demographics, breast cancer history, baseline disease characteristics, and patient treatment history. Data will be summarized by the treatment arm to which patients were randomized.

Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented by treatment arm 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.

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

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

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.

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, excluding world region, 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.

6.4.2 Secondary Efficacy Endpoints

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

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 ORR and its 95% CI (Wilson score confidence interval) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified according to the factors specified in Section 4.2.2 (excluding world region) 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.

PFS as determined by a blinded independent central review committee

Following the Sponsor's decision to prematurely terminate the study, this endpoint will not be analyzed.

PFS in patients with baseline brain metastases

PFS as defined above in the subset of patients with brain metastases at baseline.

OS in patients with baseline brain metastases

OS as defined above in the subset of patients with brain metastases at baseline.

CNS progression-free survival

CNS progression-free survival (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. 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 analysis of CNS-PFS will follow the same methodology as the PFS primary endpoint. CNS-PFS will be analyzed in the subgroups of patients with or without CNS metastases at baseline.

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.

Patient-Reported Outcomes Analysis (Secondary and Exploratory Endpoints)

Following the Sponsor's decision to prematurely terminate the study, the analysis of PRO data from the EORTC QLQ-C30 and BR23 questionnaire will no longer be performed.

6.4.3 Exploratory Efficacy Endpoints

Following the Sponsor's decision to prematurely terminate the study, the analysis of exploratory efficacy endpoints will no longer be performed.

6.5 SAFETY ANALYSES

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.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, Vital Sign, and ECG Data

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

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to NCI CTCAE v5.0. All AEs, SAEs, AEs leading to death, AESI, and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent AEs) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.5.2 Exploratory Analyses of PRO-CTCAE Data

Exploratory analyses of PRO CTCAE data will not be performed following the Sponsor's decision to prematurely terminate the study.

6.6 PHARMACOKINETIC ANALYSES

No PK analyses will be performed following the Sponsor's decision to prematurely terminate the study.

6.7 IMMUNOGENICITY ANALYSES

No ADA analyses will be performed following the Sponsor's decision to prematurely terminate the study.

6.8 BIOMARKER ANALYSES

Some descriptive biomarker analyses will be performed. Further details can be found in the SAP.

6.9 HEALTH STATUS UTILITY ANALYSES

The EQ-5D-5L will be scored according to its manual (van Reenen and Janssen 2019). Absolute score and change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated over time.

No health status utility analyses will be performed following the Sponsor's decision to prematurely terminate the study.

6.10 INTERIM ANALYSES

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

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor or with an online ePRO completion tool (see Section 7.3 for details). Sites will be responsible for entering PRO data collected by telephone (see Section 4.5.9.1) into the electronic device or the online ePRO completion tool.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The

data will be transmitted to a centralized database maintained by the electronic device vendor. For PRO assessments that are completed at home (see Appendix 3), an online ePRO completion tool will be used.

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, medication inventory records, and images must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws. Studies conducted in China will be in accordance with the approved local Informed Consent Form and applicable laws and will comply with the approved HGRAC (Human Genetics Resources Administration of China) main and exploratory applications (when applicable).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as the Prescreening Informed Consent Form) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S.

Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.4).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require

reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., AE rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits are provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor or designated, region specific, service providers will provide clinical operations management, medical monitoring and pharmacovigilance support. Data Management will be provided by the Sponsor’s Data Management provider.

Patient enrollment and treatment assignment will be handled through an interactive voice or web-based response system (IxRS). Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests, PK and biomarker analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected. An independent review facility will be used to collect and retain copies of tumor assessment scans for centralized review.

A Steering Committee (SC) will be set up to provide guidance on the protocol, study design and the SAP, and to provide guidance on review of any relevant study-related documents or procedures in order to be confident that the data collected will be timely, accurate and complete. A separate SC Charter will outline the committee’s composition, meeting timelines and the members’ roles and responsibilities.

An iDMC composed of a group of independent experts external to the Sponsor, with the aid of an independent Data Coordinating Center (iDCC), will be installed to monitor

unblinded patient safety data and blinded efficacy data during course of the study. The iDMC members will not be Principal Investigators for the study. A separate iDMC Charter will detail the committee's composition, meeting timelines, and the members' roles and responsibilities.

An independent review facility will collect, store, and review imaging data.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/*innovation/process/clinical-trials/data-sharing/*

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data (including data from analyses of study samples donated to the RBR) that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

[FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Rockville (MD): U.S. Department of Health and Human Services Food and Drug Administration; 2007 May.

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Adams S, Diamond J, Hamilton E, et al. Safety and clinical activity of atezolizumab (anti-PDL1) in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer [abstract]. Cancer Res 2015;76 (Suppl 4).

Adunlin G, Cyrus JW, Dranitsaris G. Correlation between progression-free survival and overall survival in metastatic breast cancer patients receiving anthracyclines, taxanes, or targeted therapies: a trial-level meta-analysis. Breast Cancer Res Treat 2015;154:591–608.

Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol 2020;38:1346–66.

Andrulis I, Bull S, Blackstein M, et al. neu/erbB-2 amplification identifies a poor-prognosis group of women with node-negative breast cancer. Toronto Breast Cancer Study Group. J Clin Oncol 1998;16:1340–9.

Atkinson TM, Li Y, Coffey CW, et al. Reliability of adverse symptom event reporting by clinicians. Qual Life Res 2012;21:1159–64.

Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106(9):1–11.

Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med 2010;362:865–9.

Baselga J, Javier Cortés J, Im SA, et al. Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in human epidermal growth factor receptor 2-positive, first-line metastatic breast cancer.J Clin Oncol. 2014 ;20:3753–61.

Baselga J, Javier Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–19.

Baselga J, Lewis Phillips GD, Verma S, et al. Relationship between tumor biomarkers and efficacy in EMILIA, a phase III study of trastuzumab emtansine in HER2-positive metastatic breast cancer. Clin Cancer Res, 2016.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen G, Gaupta R, Petrik RS, et al. A feasibility study of cyclophosphamide, trastuzumab, and an allogeneic GM-CSF-secreting breast tumor vaccine for HER2+ metastatic breast cancer. Cancer Immuno Res 2014;2:949–61.

Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011;29:89–96.

Cortes J, Cescon DW, Rugo HS, et al. KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. J Clin Oncol 2020;38(suppl 15; abstr 1000).

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603.

Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:732–42.

Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 2015;1:1051–9.

Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;2:228–47.

Emens LA, Braiteh FS, Cassier P. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer. Presented at: 2015 AACR Annual Meeting; April 18-22; Philadelphia, PA. Abstract 6317.

Emens LA, Esteva F, Beresford M, et al. Results from KATE2, a randomized phase 2 study of atezolizumab (atezo)+trastuzumab emtansine (T-DM1) vs placebo (pbo)+T-DM1 in previously treated HER2+ advanced breast cancer (BC). Cancer Res 2019a;79(4 Suppl):Abstract nr PD3-01.

Emens LA, Esteva F, Beresford M, et al. Overall survival in KATE2: a phase 2 study of PD-L1 inhibitor atezolizumab + trastuzumab emtansine (T-DM1) vs placebo + T-DM1 in previously treated HER2-positive advanced breast cancer. Ann Oncol 2019b;30(suppl_5): v104–v142.

Emens LA, Adams S, Barrios CH, et al. LBA16 IMpassion130: Final OS analysis from the pivotal phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. Ann Oncol 2020;31:S1148.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man [resource on the Internet]. 2012 Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC50013.

European Medicines Agency. Appendix 1 to the Guideline on the evaluation of anticancer medicinal products in man - Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. CHMP/27994/2008 Rev. 1. 01 July 2013. Available at https://www.ema.europa.eu/en/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37:1331–4.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485–99.

Fromme EK, Eilers KM, Mori M, et al. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol 2004;22:348–90.

Gennari A, André F, Barrios CH, et al.; ESMO Guidelines Committee. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475□95.

Gettinger SN, Kowanetz M. Molecular correlates of PD-L1 status and predictive biomarkers in patients with non-small cell lung cancer (NSCLC) treated with the anti–PDL1 antibody MPDL3280A. Mini oral abstract session presented at the International Association for the Study of Lung Cancer 15th World Conference; 27–30 October 2013; Sydney, Australia. Session MO19.09.

Giordano SH, Temin S, Chandarlapaty S, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018;36:2736–40.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Ann Rev Immunol 2008;26:677–704.

Krop IE, Kim SB, González-Martín A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689–99.

Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol 2017;18:743–54.

Li L, Pan Z. Progression-free survival and time to progression as real surrogate end points for overall survival in advanced breast cancer: A meta-analysis of 37 trials. Clin Breast Cancer 2018;18:63–70.

Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;19:4265–74.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

Müller P, Kreuzaler P, KhanT, et al. Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. Sci Transl Medi. 2015;7:315.

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Cancer. 2014;2:17.

Nishino M, Giobbie-Hurder A, Gargano A et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimentional measurements. Clin Cancer Res. 2013;14:3936–43.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44.

Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer. 2004;5:63–9.

[NCCN] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer. Version 2.2022. December 20 2021. 2021a [cited 17 January 2022]. Available from www.NCCN.org.

[NCCN] National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 Vaccination Advisory Committee [resource on the internet]. 2021b [cited: 28 May 2021]. Available from https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf?sfvrsn=b483da2b_2.

Pakhomov SV, Jacobsen SJ, Chute CG, et al. Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care 2008;14:530–9.

Pauletti G, Dandekar S, Rong H, et al. Assessment of methods for tissue-based detection of the HER-2/neu alteration in human breast cancer: a direct comparison of fluorescence in situ hybridization and immunohistochemistry. J Clin Oncol 2000;18:3651–64.

Primary Clinical Study Report - WO30085 - 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. Report No. 1087133; December, 2018.

Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. J Natl Cancer Inst 2011;103:185–8.

Reese DM, Slamon DJ. HER-2/neu signal transduction in human breast and ovarian cancer. Stem Cells. 1997;15:1−8.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rubin I, Yarden Y. The basic biology of HER2. Ann Oncol 2001;12(Suppl 1):S-8.

Schmid P, Adams S, Rugo HS, et al.; IMpassion130 Trial Investigators. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2108–121.

Schmid P, Rugo HS, Adams S, Schneeweiss A, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:44–59.

[SITC] Society for Immunotherapy of Cancer. Society for Immunotherapy of Cancer statement on SARS-CoV-2 vaccination and cancer immunotherapy [resource on the internet]. Press release: 23 December 2020 [cited: 28 May 2021]. Available from: https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy.

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92.

Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/*neu* oncogene. Science 1987;235:177–82.

Spigel DR, Chaft JE, Gettinger S, et al. FIR: Efficacy, safety, and biomarker analysis of a Phase II open-label study of atezolizumab in PD-L1-selected patients with NSCLC. J Thorac Oncol 2018;13:1733–42.

Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756–68.

Stagg J, Loi S, Divisekera U, et al. Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy. Proc Natl Acad Sci U S A 2011;108:7142–47.

Stone A, Gebski V, Davidson R, et al. Exaggeration of PFS by blinded, independent, central review (BICR). Ann Oncol 2019;30:332–8.

Toikkanen S, Helin H, Isola J, et al. Prognostic significance of HER-2 oncoprotein expression in breast cancer: a 30-year follow-up. J Clin Oncol 1992;10:1044–8.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Trotti A, Pajak TF, Gwede CK, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. Lancet Oncol 2007;8:613–24.

van Reenen M, Janssen B. EQ-5D-5L User guide. Basic information on how to use the EQ-5D-5L instrument. Version 3.0, September 2019. https://euroqol.org/publications/user-guides/.

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Eng J Med 2012;367:1783–91.

von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380:617–28.

Waks AG, Winer EP. Breast cancer treatment: A review. JAMA 2019;321:288–300.

Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;23:7412–20.

Wolff AC, Hammond ME, Hicks DG et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013.

Wolff AC, Hammond ME, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 2018; 142:1364–82.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Zhang H, Zhang S, Wang Y, et al. Re-evaluation of HER2 status in 1 501 invasive breast cancers according to the 2013 American Society of Clinical Oncology/College of American Pathology guidelines. 2015;44:42 – 7.

Appendix 1 Schedule of Activities

Assessment or Procedure	Screening [a]	Treatment Period (21-Day Cycles) (Cycles 1 through Study Treatment Discontinuation)	Study Treatment Completion/Early Discontinuation	Follow-Up [b]
	Days −28 to −1	Day 1 of each cycle (± 3 Days) unless otherwise indicated	28–42 days after Last Dose	
Informed consent [c]	x			
Demographics [d]	x			
Medical history [e]	x			
HER2 and PD-L1 testing [f]	x			
Complete physical examination [g]	x			
Limited physical examination [h]		x [ee]	x	
ECOG performance status	x	x	x	
Height	x			
Weight [i]	x	x		
Vital signs [j]	x	x [ee]	x	
Hematology [k]	x [l]	x [m, ee]	x	*x* [ff]
Serum chemistry [n]	x [l]	x [m, ee]	x	*x* [ff]
TSH, free T3 (or total T3), free T4 [o]	x	x [o]	x	*x* [ff]
Coagulation (INR, aPTT)	x [l]	As clinically indicated		
HIV, HCV, and HBV serology [p]	x			
Urinalysis [q]	x	As clinically indicated		
Pregnancy test [r]	x	x	x	x
C-reactive protein	x			
Tumor and response assessment [s]	x	x [t]		x [t]

Appendix 1: Schedule of Activities (cont.)

Assessment or Procedure	Screening [a]	Treatment Period (21-Day Cycles) (Cycles 1 through Study Treatment Discontinuation)	Study Treatment Completion/Early Discontinuation	Follow-Up [b]
	Days −28 to −1	Day 1 of each cycle (± 3 Days) unless otherwise indicated	28–42 days after Last Dose	
Bone scan/PET [u]	x	As clinically indicated		
CT or MRI of brain [v]	Mandatory at screening	As clinically indicated or as scheduled tumor assessment [v]		
ECG (12-lead) [w]	x	As clinically indicated		
NYHA classification	x			
ECHO or MUGA scan [x]	x	x Day 15–21 of Cycle 1, Day 15–21 of every fourth cycle thereafter, and as clinically indicated	x If not performed within 6 weeks prior to this visit	*x ff*
Atezolizumab/placebo administration [y]		x		
Trastuzumab emtansine administration [y]		x		
PROs: QLQ-C30, EORTC Treatment Burden Item, QLQ-BR23, EQ-5D-5L, PRO-CTCAE [z]		x (See Appendix 3)	x (See Appendix 3)	x (See Appendix 3)
PK/ADA		x (See Appendix 2)	x (See Appendix 2)	
Blood samples for biomarker analysis		x (See Appendix 2)	x (See Appendix 2)	
Sample for auto-antibodies [aa]	X			
Tissue sample for biomarker analysis	x (See Appendix 2)		x (See Appendix 2) [bb]	
Concomitant medications	X	x	x	
Adverse events [cc]	x	x [ee]	x	x
Survival follow-up [dd]				x
Initiation of anti-cancer treatments [dd]			x	x

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; SOC = standard of care; 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.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such assessments do not need to be repeated for screening.

[b] The follow up period begins from the date of treatment completion / early termination visit. Visits will be conducted every 3 months, until the study end. Visits windows are +/-14 days for all follow up visits.

[c] Informed consent by the patient or the patient's legally-authorized representative must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

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

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

[f] Conducted in the central laboratory. If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. Refer to Appendix 2 for tissue sample requirements. For patients who sign the separate prescreening informed consent form, these assessments can be made in the central laboratory (using archival tissue only) up to 12 months before randomization. Up to two prescreening samples can be sent for analysis (i.e., if the first sample fails the prescreening, a second one can be sent). If a patient consents to prescreening for determination of HER2 and PD-L1, these tests would not need to be repeated during the screening period. If patients are being rescreened, then HER2 and PD-L1 testing do not need to be repeated.

[g] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events 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 to determine if the dose of trastuzumab emtansine should be adjusted (see Section 4.3.2.1).

[j] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. See Section 4.5.4 for guidance on timing

for vital sign measurements for first and subsequent infusions of trastuzumab emtansine and atezolizumab/placebo. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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

[l] Specified screening laboratory tests must be obtained within 7 days prior to initiation of study treatment. Results must be reviewed and documented prior to administration of the first dose of study treatment.

[m] Specified laboratory tests must be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before [up to 7 days before for Cycle 1, Day 1]).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[o] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

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

[q] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood; dipstick permitted.

[r] All women of childbearing potential will have a serum pregnancy test within 7 days prior to initiation of study treatment. Urine or serum pregnancy tests will be performed every cycle, within 3 days prior to study treatment administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. All patients will have a urine or serum pregnancy test at the study completion/early termination visit and at 3 months (± 28 days) and 7 months (± 28 days) after the last dose of trastuzumab emtansine.

[s] All measurable (and non-measurable) lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined in Section 4.5.5. Screening assessments must include CT scans with contrast or MRI scans of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. A bone scan (or other suitable modality for bone imaging, e.g., NaF or FDG-PET) will also be performed at screening. If clinically indicated, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[t] Patients will undergo tumor assessments at baseline (screening) and then every 6 weeks (± 7 days) following treatment initiation, regardless of dose delays, until investigator-assessed radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new anti-cancer therapy, until disease progression. All measurable (and non-measureable) lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Brain scans (preferably MRI) must be conducted at all subsequent tumor evaluations in patients with known brain metastases. Patients without brain metastases at baseline should have brain scans (preferably MRI) as clinically indicated. A bone scan (or other suitable modality for bone imaging e.g., NaF or FDG-PET) should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions. Tumor response will be evaluated using RECIST v1.1 (Appendix 4). *Tumor assessments may be done according to standard of care at the site, following premature study termination.*

[u] A 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.

[v] CT/MRI scan of the brain is mandatory at screening and should be performed 1) with scheduled tumor assessments when identified as a site of involvement at baseline, 2) as clinically indicated.

[w] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[x] 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.

[y] 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. 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.

[z] Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of all other assessments, and prior to the administration of study treatment (See Appendix 3). Laboratory and weight assessments can be completed before the PROs are administered; however, the results of these assessments should not be given to the patient prior to completing the PROs. *PROs do not need to be collected after premature study termination.*

[aa] Auto-antibody testing includes anti-nuclear antibody, anti–double-stranded DNA, and circulating and perinuclear cytoplasmic antibody. The baseline sample will be collected prior to the first dose of study drug on Cycle 1, Day 1. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally, if necessary. *Samples no longer need to be collected after premature study termination.*

[bb] 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), if deemed clinically feasible and the patient would not be put at risk, as assessed by the investigator.

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

[dd] After treatment discontinuation, information on survival status and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or the Sponsor terminates the study. Study staff may use a public information source (e.g., county records) to obtain information about survival status only. *Following the announcement of premature study termination, data on survival and new anti-cancer therapies will no longer be collected.*

[ee] In addition to Day 1, the following assessments will also be conducted on Day 10 (±3 days) of Cycle 1 and Cycle 2: limited physical examination, vital signs, hematology, serum chemistry, and adverse events.

ff To be performed if patient has unresolved AEs at the time of treatment discontinuation and/or if clinically indicated. If patients are already in follow-up, it is recommended that patients in follow-up return to the site for a final visit before being discontinued from the study.

Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

CONTENTS

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

Visit	Timepoint	Sample Type[c]
Cycle 1, Day 1 and Cycle 4 Day 1	Pre-infusion of atezolizumab or placebo[b]	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ADA 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 of atezolizumab or placebo[b]	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ADA to atezolizumab[c]
Study treatment completion/early discontinuation visit	At any time during visit	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ADA to atezolizumab

ADA = anti-drug antibody, also called anti-therapeutic antibody; PK = pharmacokinetic.

[a] Due to double-blinded study design, the samples should be collected for both treatment arms but analyses will only be conducted for patients randomized to the trastuzumab emtansine plus atezolizumab arm. *Samples are no longer to be collected after the Sponsor's decision for premature study termination.*

[b] Within 24 hours prior to atezolizumab or placebo infusion.

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

Table 2 Anti-Drug Antibody and Pharmacokinetic Assessments for Trastuzumab Emtansine for Arm A and Arm B

Visit	Timepoint	Sample Type
Cycle 1, Day 1 and Cycle 4 Day 1	Pre-infusion of trastuzumab emtansine [a]	Serum sample for trastuzumab emtansine pharmacokinetics Serum sample for total trastuzumab pharmacokinetics
		Serum sample for ADA 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 pharmacokinetics Serum sample for total trastuzumab pharmacokinetics Plasma sample for DM1 pharmacokinetics
Cycle 2, Day 1	Pre-infusion of trastuzumab emtansine [a]	Serum sample for trastuzumab emtansine pharmacokinetics Serum sample for total trastuzumab pharmacokinetics
Study treatment completion /early discontinuation visit	At any time during visit	Serum sample for trastuzumab emtansine pharmacokinetics Serum sample for total trastuzumab pharmacokinetics
		Serum sample for ADA to trastuzumab emtansine

[a] Within 24 hours prior to trastuzumab emtansine infusion. *Samples are no longer to be collected after the Sponsor's decision for premature study termination.*

Table 3 Blood Samples for Biomarker Analysis

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pre-infusion	Blood sample for WGS/WES [a,b]
		Plasma sample for biomarkers
Cycle 2, Day 1	Pre-infusion	Plasma sample for biomarkers
Cycle 3, Day 1	Pre-infusion	Plasma sample for biomarkers
Cycle 8, Day 1	Pre-infusion	Plasma sample for biomarkers
Cycle 16, Day 1	Pre-infusion	Plasma sample for biomarkers
Disease Progression	At any time during visit	Plasma sample for biomarkers

[a] Not applicable for a site that has not been granted approval for WGS/WES.

[b] If missed on Day 1, this blood sample can be collected at any point in the study. *Samples are no longer to be collected after the Sponsor's decision for premature study termination.*

Table 4 Tissue Sample for Biomarker Analysis

Visit	Timepoint	Sample Type
Screening (mandatory)	Pre-infusion	Preferred: FFPE archival tumor block (most recently collected, available tumor tissue) or FFPE fresh tumor block (at least 3 cores, embedded in a single paraffin block). In case of site regulations that prevent sending a paraffin block, at least 17 slides (9 slides for screening tests and 8 slides for additional biomarker tests) containing unstained, freshly cut, serial sections must be submitted. The unstained slides for staining must be within the current documented cutslide stability window. Leftover slides after screening tests may also be used for additional biomarker tests. The sample needs to be of good quality based on total and viable tumor content. 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. In case of submission of lesions from left and right breast: a representative FFPE tumor specimen in a paraffin block of each lesion is preferred (if slides are provided: at least 9 slides containing unstained, freshly cut, serial sections are required from each lesion for screening tests. In addition to this requirement, a total of 8 slides are required for the additional biomarker tests. Preferably, these additional 8 slides are derived from the lesion which was determined HER2 and 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, provide 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. A representative FFPE tumor specimen in a paraffin block of all lesions (preferred) or at least 9 slides are required from each lesion. In addition to this requirement, a total of 8 slides is required for the remaining biomarker tests. Preferably, these additional 8 slides are derived from the lesion which was determined HER2 and PD-L1-positive. • For multifocal tumors at least one focus is centrally confirmed as HER2-positive and PD-L1 positive. – A representative FFPE tumor specimen in a paraffin block (preferred) or at least 17 slides containing unstained, freshly cut, serial sections must be submitted.

Appendix 2: Schedule of PK, Immunogenicity, and Biomarker Samples (cont.)

Visit	Timepoint	Sample Type
Disease progression (if deemed clinically feasible and the patient would not be put at risk)	Must be taken before next line of therapy begins. [a] In case new line therapy is purely anti-hormonal, biopsy could be taken after it is started.	Fresh core biopsy (preferably 3 cores) at site of progression if accessible or from any other lesion. A representative FFPE tumor specimen in a paraffin block (preferred) or a minimum of 10 slides containing unstained, freshly cut, serial sections must be submitted.

[a] Within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner.

Appendix 3 Schedule of Patient-Reported Outcome Assessments

Questionnaires will be self-administered before the patient receives any information on disease status, prior to the performance of all other assessments, and prior to the administration of study treatment. *PRO assessments are no longer to be collected after the Sponsor's decision for premature study termination.*

TIMING OF PRO ASSESSMENTS

PRO [a]	**Treatment period** (Cycle 1 through study treatment discontinuation) **Cycles (Day 1 unless otherwise indicated)**														**Study treatment completion / Early discontinuation visit** 28–42 days after last dose	**Follow-up** 3 months after study treatment completion / Early discontinuation visit
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**			
EORTC QLQ-C30 (Appendix 10) and EQ-5D-5L (Appendix 12)	x	X	x		x		x		x		x		x	Every **second** cycle thereafter	x	x
EORTC Treatment Burden Item (Appendix 14)	x	X	x		x		x		x		x		x	Every second cycle thereafter	x	x
EORTC QLQ-BR23 [b] (Appendix 11)	x		x		x				x				x	Every **fourth** cycle thereafter	x	x
NCI PRO-CTCAE (Appendix 13)	x 3[c]	x 3[c]	x 3[c]		x		x		x		x		x	Every **second** cycle thereafter	x	x

Appendix 3: Schedule of PRO assessments

[a] PROs should be administered on planned Day 1 of the indicated cycles, except where indicated. The Day 1 PROs for any cycle are not to be completed again in the event that it is determined following completion of the PROs that the treatment on Day 1 of the given treatment cycle will be delayed. Additionally, the timing of any subsequent PRO assessments will be based on the actual Day 1 of the given cycle (e.g., if it is determined that the start of treatment at Cycle 3 will be delayed a week, the Day 8 PRO-CTCAE will occur one week after the start of treatment, and the Cycle 4 Day 1 assessment will occur when the next Day 1 administration of treatment is planned).

[b] On days when both the QLQ-C30 and QLQ-BR23 are administered, the QLQ-BR23 must be administered immediately after the QLQ-C30.

[c] PRO-CTCAE items are completed three times (on Day 1, Day 8, and Day 15) for the indicated cycles. The patient should complete the PRO-CTCAE assessments on Day 8 and Day 15 of Cycles 1, 2, and 3 at home using the online ePRO completion tool. If the patient does not have access to the online ePRO completion tool at home and cannot come to the study site to use the electronic device, the site can call the patient and collect the PRO-CTCAE assessments on Day 8 and Day 15 of Cycles 1, 2, and 3 by telephone. The telephone is not to be used to collect PRO data at any other timepoint.

Appendix 4 Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions and lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lungs, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, positron emission tomography (PET) scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and not usually more than 4 weeks prior to the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without MRI IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (with or without MRI IV contrast) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, AND HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20×30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, given that a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce During Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining the maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in the short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "unequivocal progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the following criteria used to determine objective tumor response for target lesions are provided:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for a CR or a PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions

  All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of

substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it truly represents new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared as of the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients.

Table 1 Criteria for Overall Response at a Single Timepoint

Target Lesions	Non-Target Lesions	New Lesions	Timepoint Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR, non-CR/Non-PD, or NE	No	PR
SD	CR, non-CR/Non-PD, or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR	NED [b]	No	CR
PR	NED [b]	No	PR
SD	NED [b]	No	SD
NED [a]	Non-CR/non-PD	No	Non-CR/non-PD
NED [a]	CR	No	CR
NED [a]	NE	No	NE
NED [a]	NED [b]	No	NED

CR = complete response; NE = not evaluable; NE = not evaluable disease;
PD = progressive disease; PR = partial response; SD = stable disease.

[a] No target lesions identified at baseline

[b] No non-target lesions identified at baseline.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging or measurement is performed at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study treatment. The

objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1 .

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Fluorodeoxyglucose (FDG)-PET is not yet validated for use in clinical trials to determine response but may complement CT/MRI in the assessment of progression.

FDG-PET imaging to identify new lesions is described in the following table.

Baseline FDG-PET	Post-Baseline FDG-PET	Determination
Negative FDG-PET	Positive FDG-PET	New lesion (PD)
None	Positive FDG-PET corresponds to a new site of disease confirmed by CT/MRI	New lesion (PD)
None	Positive FDG-PET not confirmed as a new site of disease on CT/MRI	Additional follow-up CT/MRI scans are needed to determine if there is truly progression occurring at that site. If so, new lesion (PD) with the date of PD being the date of the initial abnormal FDG-PET scan date If not, it is not a new lesion.
None	Positive FDG-PET that corresponds to a preexisting site of disease on CT/MRI that is not progressing on the basis of the anatomic images	Not a new lesion

CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography.
Note: A positive FDG-PET scan lesion indicates one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Schwartz LH., Litiére S, de Vries SE, et al. RECIST 1.1–update and clarification: from RECIST Committee. Eur J Cancer 2016; 62:132–7.

Appendix 5 Ventana HER2 IHC Assay

VENTANA anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody (VENTANA HER2 (4B5) antibody) is intended for the semi-quantitative detection of HER2 antigen in sections of formalin-fixed, paraffin-embedded normal and neoplastic breast and gastric tissue on a BenchMark IHC/ISH instrument.

This product is indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin treatment is considered and for breast cancer patients for whom KADCYLA® (ado-trastuzumab emtansine) or PERJETA® (pertuzumab) treatments are being considered.

This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

This antibody is intended for *in vitro* diagnostic (IVD) use.

DEVICE DESCRIPTION

VENTANA HER2 (4B5) antibody is a rabbit monoclonal antibody, which binds to HER2 in paraffin-embedded tissue sections. The specific antibody can be localized by either a biotin conjugated secondary antibody formulation that recognizes rabbit immunoglobulins followed by the addition of a streptavidin-horseradish peroxidase (HRP) conjugate (iVIEW DAB Detection Kit) or a secondary antibody-HRP conjugate (ultraView Universal DAB Detection Kit). The specific antibody-enzyme complex is then visualized with a precipitating enzyme reaction product. Each step is incubated for a precise time and temperature. At the end of each incubation step, the BenchMark IHC/ISH instrument washes the sections to stop the reaction and to remove unbound material that would hinder the desired reaction in subsequent steps. It also applies Liquid Coverslip, which minimizes evaporation of the aqueous reagents from the specimen slide.

Clinical cases should be evaluated within the context of the performance of appropriate controls. Ventana recommends the inclusion of a positive tissue control fixed and processed in the same manner as the patient specimen (for example, a weakly positive breast or gastric carcinoma). In addition to staining with VENTANA HER2 (4B5) antibody, a second slide should be stained with CONFIRM Negative Control Rabbit Ig. For the test to be considered valid, the positive control tissue should exhibit membrane staining of the tumor cells. These components should be negative when stained with CONFIRM Negative Control Rabbit Ig. In addition, it is recommended that a negative tissue control slide (for example, a HER2 negative breast or gastric carcinoma) be included for every batch of samples processed and run on the BenchMark IHC/ISH instrument. This negative tissue control should be stained with VENTANA HER2 (4B5) antibody to ensure that the antigen enhancement and other pretreatment procedures did not create false positive staining.

Details of the staining protocol and scoring criteria can be found in instruction for use and interpretation guide published by Ventana Medical Systems Inc. (https://dialog.roche.com)

Appendix 6 Ventana HER2 Dual ISH DNA Probe Cocktail

The VENTANA HER2 Dual ISH DNA Probe Cocktail is intended to determine *HER2* gene status by enumeration of the ratio of the *HER2* gene to Chromosome 17 by light microscopy. The HER2 and Chromosome 17 probes are detected using two-color chromogenic in situ hybridization (ISH) in formalin-fixed, paraffin embedded human breast carcinoma tissue specimens, following staining on the Benchmark ULTRA instruments.

The VENTANA HER2 Dual ISH DNA Probe Cocktail is indicated as an aid in the assessment of patients for whom HER2-directed therapy is being considered. This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

DEVICE DESCRIPTION

The VENTANA HER2 Dual ISH DNA Probe Cocktail is optimally formulated for use with VENTANA Silver ISH DNP Detection Kit, VENTANA Red ISH DIG Detection Kit, and accessory reagents on a BenchMark IHC/ISH instrument.

The detection kit contains a primary antibody and an enzyme-labeled secondary antibody conjugated to horseradish peroxidase (HRP) or alkaline phosphatase (ALP) which is used as the chromogenic enzyme. During the Dual in situ hybridization (Dual ISH) staining process, DNP and DIG labeled probes are co-hybridized to their respective specific target DNA sequences within the cell nuclei. Detection of the DNP-labeled HER2 probe occurs first, using the VENTANA Silver ISH (SISH) DNP Detection Kit, which contains the following dispensers: mouse anti-DNP primary antibody labeled with hydroxyquinoxaline (HQ), mouse anti-HQ secondary antibody conjugated to horseradish peroxidase (HRP), Chromogen A (Silver A), Chromogen B (Silver B) and Chromogen C (Silver C). Following incubation with the HQ-labeled mouse anti-DNP primary antibody and then mouse anti HQ HRP secondary antibody conjugate, the SISH reaction occurs. Briefly described, this reaction is driven by the sequential addition of Chromogens A (silver acetate), B (hydroquinone) and C (H2O2). Here, the silver ions (Ag+) are reduced by hydroquinone to metallic silver atoms (Ag0). This reaction is fueled by the substrate for HRP, hydrogen peroxide (Chromogen C). The silver precipitate is deposited in the nuclei and a single copy of the *HER2* gene is visualized as a black dot.

Following SISH detection for *HER2*, the DIG-labeled Chromosome 17 probe is detected with the ultraView Red ISH DIG Detection Kit. This kit includes the following dispensers: a mouse anti-DIG monoclonal antibody, Red ISH Multimer solution which contains a goat anti-mouse IgG antibody conjugated to ALP, pH Enhancer, Naphthol, and Fast Red. Following development of the SISH signal, the slide is incubated with the mouse

anti-DIG antibody, which binds to the DIG hapten on the Chromosome 17 probe. The anti-hapten primary antibody is detected with the Multimer solution (goat anti-mouse IgG conjugated to ALP enzyme). The slide is incubated with the pH Enhancer solution which provides the proper salt components/concentrations and buffered pH for optimal ALP enzyme performance. Next, naphthol phosphate is applied, which serves as the substrate for the ALP enzyme (ALP dephosphorylates naphthol). Fast Red, added to the slide next, combines with the dephosphorylated naphthol to form a red precipitate, which is readily visualized by light microscopy. The specimen is then counterstained with Hematoxylin II for interpretation by light microscopy.

The staining protocol consists of numerous steps in which reagents are incubated for pre-determined times at specific temperatures. At the end of each incubation step, the BenchMark ULTRA instrument washes the sections to remove unbound material and applies a liquid coverslip which minimizes the evaporation of the aqueous reagents from the slide. Results are interpreted using a light microscope.

Details of the staining protocol and scoring criteria can be found in the investigational instructions for use included with the associated diagnostic study protocol.

BENEFIT-RISK ASSESSMENT

The CE-marked VENTANA HER2 Dual ISH DNA Probe Cocktail is indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) is being considered but is investigational as an aid in the assessment of patients for whom HER2-directed therapy is being considered, including trastuzumab emtansine.

As with any diagnostic test, there is possibility for an incorrect test result when determining the HER2 expression level for a patient tumor specimen. The potential impact to patients associated with false test results must be considered both in light of the safety profile of the investigational therapeutic product and the potential for clinical benefit from therapeutic product exposure.

The consequence of a false HER2 negative status result is that a patient would be erroneously excluded from enrolling into the study and would not receive the potential clinical benefit imparted by investigational HER2-targeted and PD-L1-targeted therapy.

The consequence of a false HER2 positive status result is that a patient may be erroneously enrolled into the treatment phase of the study. In this case, the patient may be subjected to the potential side effects of the investigational therapy combination of trastuzumab emtansine plus atezolizumab/placebo and may not experience any additional clinical benefit beyond what they would have experienced with standard of care.

The analytical performance of VENTANA HER2 Dual ISH DNA Probe Cocktail has been validated for its intended use within the context of this clinical study. Analytical

performance testing included sensitivity, robustness, repeatability and reproducibility in staining HER2 DNA target sequences in breast carcinoma tissue, as well as reader precision using the scoring algorithms. The results of the analytical performance testing demonstrated that the assay robustly and specifically stains the HER2 targets in breast carcinoma tissue and that trained pathologists can assess and score HER2 expression with precision according to the scoring algorithms.

The VENTANA HER2 Dual ISH DNA Probe Cocktail utilizes the presence of normal HER2 and Chromosome 17 signals (1 to 2 copies per cell) as an internal positive control to minimize potential of a false result.

Note the following factors that mitigate the risk of a false positive HER2 ISH result in Study MO42319:

All patient samples will be tested for HER2 expression by both the investigational VENTANA HER2 Dual ISH DNA Probe Cocktail and the VENTANA anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody IHC assay, which is CE marked for the identification of breast carcinoma patients for treatment with trastuzumab emtansine.

VENTANA HER2 Dual ISH DNA Probe Cocktail is CE marked to identify patients for treatment with trastuzumab, which has a similar binding affinity with trastuzumab emtansine for HER2.

Furthermore, all enrolled patients will be closely monitored for adverse events and evidence of disease progression.

Risks have been analyzed per ISO14971. All possible residual risks associated with the identified hazards and harms to the operator/patients have been reduced as far as possible by the controls implemented during the design and development of the product.

The benefit-risk ratio of the companion diagnostic investigational product is expected to be acceptable in this study.

Appendix 7 Ventana PD-L1 (SP142) Assay

VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody is intended for the qualitative immunohistochemical assessment of the programmed death ligand 1 (PD-L1) protein in formalin-fixed, paraffin-embedded (FFPE) breast carcinoma (BC) tissue stained with a BenchMark ULTRA instrument. It is indicated as an aid in identifying patients eligible for treatment with therapy targeting the interaction of PD-1 and PD-L1.

The clinical interpretation of any staining, or the absence of staining, must be complemented by histological studies and evaluation of proper controls. Evaluation must be made by a qualified pathologist within the context of the patient's clinical history and other diagnostic tests.

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

DEVICE DESCRIPTION

VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody assay (VENTANA PD-L1 (SP142) assay) utilizes VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody (VENTANA PD-L1 (SP142) antibody) to recognize the PD-L1 protein. This assay is being developed as a companion diagnostic for identifying patients with breast carcinoma eligible for treatment with therapy targeting the interaction of PD-1 and PD-L1.

Details of the staining protocol and scoring criteria can be found in the investigational instructions for use included with the associated diagnostic study protocol.

VENTANA PD-L1 (SP142) assay utilizes a rabbit monoclonal primary antibody which binds to PD-L1 in paraffin-embedded tissue sections. The specific antibody can be localized using OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001) followed by OptiView Amplification Kit (Cat. No. 760-099 / 06396518001 (50 test) or 860-099 / 06718663001 (250 test)). Refer to the appropriate OptiView DAB IHC Detection Kit and OptiView Amplification Kit package inserts for further information (https://diagnostics.roche.com).

BENEFIT-RISK ASSESSMENT

The CE-marked VENTANA PD-L1 (SP142) Assay is indicated as an aid for identifying patients for treatment with TECENTRIQ (atezolizumab) in indications such as Triple-Negative Breast Carcinoma (TNBC) but is considered investigational for HER2- positive breast cancer.

As with any diagnostic test, there is possibility for an incorrect test result when determining the PD-L1 expression level for a patient tumor specimen. The potential impact to patients associated with false test results must be considered both in light of

the safety profile of the investigational therapeutic product and the potential for clinical benefit from therapeutic product exposure.

The consequence of a false PD-L1 negative status result is that a patient would be erroneously excluded from enrolling into the study and would not receive the potential clinical benefit imparted by investigational HER2-targeted and PD-L1-targeted therapy.

The consequence of a false PD-L1 positive status result is that a patient may be erroneously enrolled into the treatment phase of the study. In this case, the patient may be subjected to the potential side effects of the investigational therapy combination of trastuzumab emtansine plus atezolizumab/placebo and may not experience any additional clinical benefit beyond what they would have experienced with standard of care.

The analytical performance of the PD-L1 (SP142) Assay has been validated for its intended use within the context of this clinical study. Analytical performance testing included sensitivity, robustness, repeatability and reproducibility in staining PD-L1 protein in breast carcinoma tissue, as well as reader precision using the scoring algorithms. The results of the analytical performance testing demonstrated that the assays robustly and specifically stain the PD-L1 targets in breast carcinoma tissue and that trained pathologists can assess and score PD-L1 expression with precision according to the scoring algorithms.

The PD-L1 (SP142) Assay requires the use of proper staining run controls, including a system level control for each run and a negative reagent control for each tissue specimen, to minimize possibility of a false result.

Furthermore, all enrolled patients will be closely monitored for adverse events and evidence of disease progression.

Risks have been analyzed per ISO14971. All possible residual risks associated with the identified hazards and harms to the operator/patients have been reduced as far as possible by the controls implemented during the design and development of the product.

The benefit-risk ratio of the companion diagnostic investigational product is expected to be acceptable in this study.

Appendix 8 New York Heart Association Classification

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

Note: Excerpted from Oxford Textbook of Medicine. Vol 2, p. 2228. Oxford Press 1997.

Appendix 9 ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 10 European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 11 EORTC QLQ-Breast Cancer Module (BR23) Questionnaire

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 12 EuroQol 5-Dimension 5 Levels Questionnaire: EQ-5D-5L

Health Questionnaire

English version

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

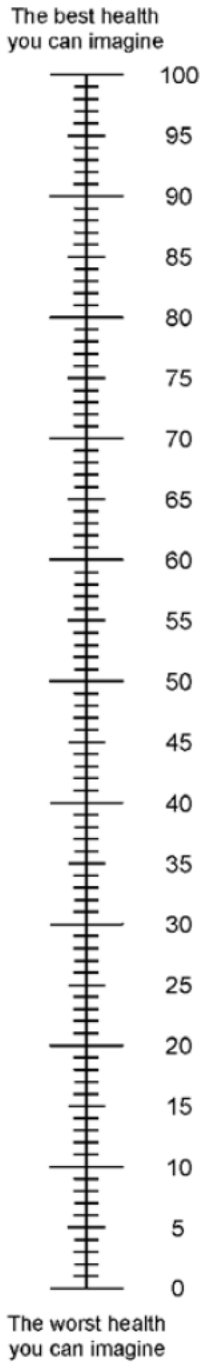
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 13 National Cancer Institute Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 25 June 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, did you have any RASH?	
O Yes	O No

3a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
3b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

4a. In the last 7 days, how OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
4c. In the last 7 days, how much did PAIN INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

5a. In the last 7 days, how OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
5b. In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
5c. In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

6a. In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
6b. In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6c. In the last 7 days, how much did ACHING MUSCLES INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
7b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9a. In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
9b. In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

OTHER SYMPTOMS				
Do you have any other symptoms that you wish to report?				
O Yes			O No	
Please list any other symptoms:				
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?			
	O None	O Mild	O Moderate	O Severe	O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?			
	O None	O Mild	O Moderate	O Severe	O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?			
	O None	O Mild	O Moderate	O Severe	O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?			
	O None	O Mild	O Moderate	O Severe	O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?			
	O None	O Mild	O Moderate	O Severe	O Very Severe

Appendix 14 Burden of Treatment Item from EORTC

During the past week:	Not at all	A little	Quite a bit	Very much
To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 15 Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Appendix 15
Preexisting Autoimmune Diseases and Immune Deficiencies (cont.)

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune myelitis* • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • *Granulomatosis with polyangiitis* • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease

Appendix 16 Guidelines for Liver Biopsy

Because nodular regenerative hyperplasia (NRH) can be a very subtle diagnosis to make on liver biopsy, every attempt should be made to maximize the amount of tissue obtained.

A minimum size of an 18-gauge needle and percutaneous biopsies of at least 1.5 cm in length are recommended if clinically appropriate. In order to diagnose NRH, reticulin and trichrome stains are necessary.

Smaller biopsies obtained via a transjugular approach as well as smaller biopsy gun needle biopsies are discouraged. Small wedge biopsies should also be discouraged.

Appendix 17 Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 18 Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine

Suggested workup and management guidelines for overlapping toxicities between atezolizumab and trastuzumab emtansine (i.e., suspected hepatotoxicity and pneumonitis) are provided in Appendix 20.

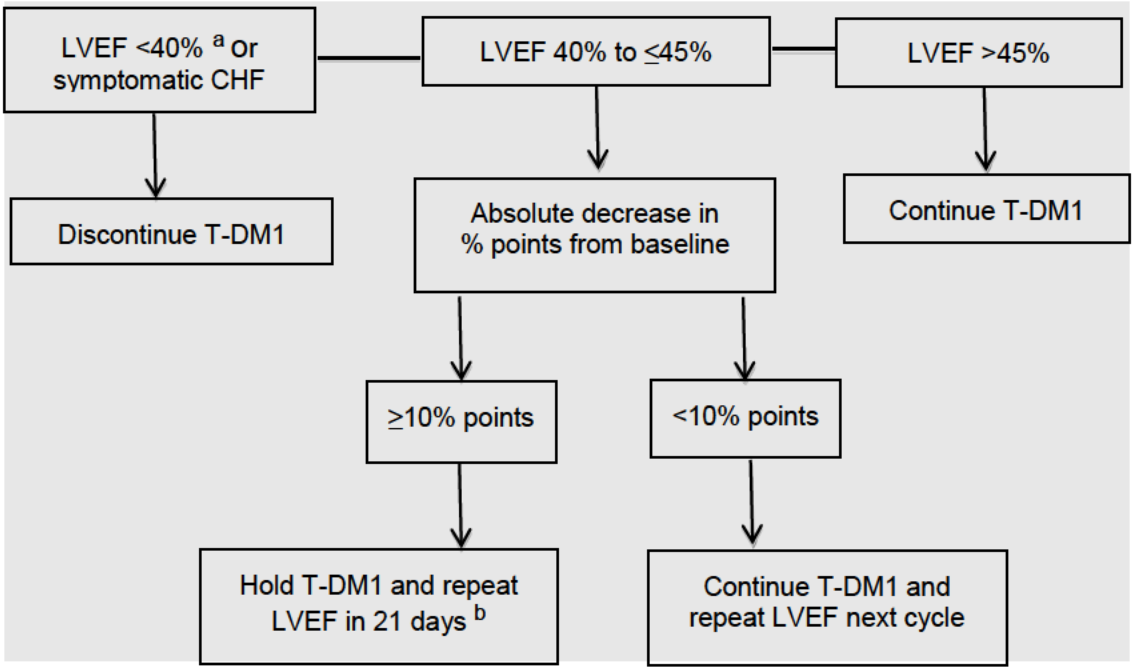
CARDIOTOXICITY

Patients without significant cardiac history and with a baseline LVEF of ≥50% as determined by ECHO or MUGA scan are eligible for study participation. Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the Study. Assessments will occur during the screening period, and on Day 15–21 of Cycle 1, and every fourth cycle thereafter. ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed ≥28 days after last study treatment administration or if no post-treatment evaluation was performed (Appendix 1).

Figure 1 summarizes the management of trastuzumab emtansine on the basis of LVEF measurements and changes in LVEF from baseline in patients. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any patient who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

The decision to stop or continue trastuzumab emtansine treatment should be on the basis of the algorithm shown in Figure 1 or asymptomatic declines in LVEF. Trastuzumab emtansine must be discontinued in all patients for whom a confirmed decrease of LVEF to <40% is documented (with a confirmation assessment carried out within 21 days). For patients whose LVEF decreases to values of 40%–45% with an absolute decrease in LVEF of ≥10% points from baseline, trastuzumab emtansine dose should be held. For these patients, the LVEF measurement should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if the LVEF has not recovered to within a 10% absolute difference below baseline. If clinically significant cardiac dysfunction or cardiac failure develops or persists or if significant medical management is required to maintain LVEF, the patient should be discontinued from all study treatment.

Figure 1 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Treatment Based on LVEF Assessments in Patients



CHF = congestive heart failure; LVEF = left ventricular ejection fraction; T-DM1 = trastuzumab emtansine.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

[a] LVEF <40% should be repeated within 21 days, and trastuzumab emtansine treatment should be discontinued if LVEF <40% is confirmed. Trastuzumab emtansine should be held while the confirmatory LVEF measurement is obtained.

[b] After a second consecutive confirmatory measurement is obtained, trastuzumab emtansine treatment should be discontinued if the ≥10% absolute LVEF decrease from baseline is confirmed.

INFUSION-RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS

See Table 1 for management guidelines for trastuzumab emtansine–associated infusion-related reactions and hypersensitivity reactions.

Table 1 Management Guidelines for Trastuzumab Emtansine Infusion-Related Reactions (Caused by Cytokine Release) or Hypersensitivity (Allergic) Reaction

Event	Action to Be Taken
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as clinically indicated. Monitor patient until complete resolution of symptoms. When symptoms have completely resolved, infusion may be restarted at no more than 50% of prior rate and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate at the next cycle, with appropriate monitoring. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given as clinically indicated.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β–agonists, antihistamines, antipyretics, or corticosteroids, as clinically indicated. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given as clinically indicated.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, as clinically indicated. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.

HEMATOLOGIC TOXICITIES

See Table 2 for trastuzumab emtansine dose modification guidelines for hematological toxicities, including thrombocytopenia.

Table 2 Trastuzumab Emtansine Dose Modification Guidelines for Hematological Toxicity

Event	Action to Be Taken
Grade 2 thrombocytopenia (50,000 to 75,0000/μL)	Assess platelet counts weekly or as medically indicated until recovery. Withhold study treatment until Grade ≤ 1. Resume treatment without dose reduction.
Grade 3 thrombocytopenia (25,000 to < 50,000/μL)	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (< 25,000/μL) at any time	Withhold trastuzumab emtansine until recovery to Grade ≤ 1 (≥ 75,000/μL). Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 1 within 42 days after the last dose received.
Grade ≥ 3 hematologic toxicity other than thrombocytopenia	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

NEUROPATHY

See Table 3 for trastuzumab emtansine dose modification guidelines for neuropathy.

Table 3 Trastuzumab Emtansine Dose Modification Guidelines for Neuropathy

Event	Action to Be Taken
Grade ≥ 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤ 2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.

Appendix 19 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5□1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1□2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. *R*esumption of atezolizumab may be considered *in patients who are* deriving benefit and *have* fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab

should be based on *the* investigator's assessment of *the benefits and risks* and documented by the investigator. The Medical Monitor is available to advise as needed.

Guidelines for managing patients who experience selected adverse events are provided in the following sections.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Appendix 20.

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Appendix 20.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 1.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 1 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 1 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 2.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 2 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status)* • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for lifethreatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*

Table 2 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for lifethreatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and the contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Table 2 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 3.

Table 3 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 4.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 4.

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 4. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 4 Management Guidelines for Immune-Mediated *Cardiac Events*

Event	Management
Immune-mediated myocarditis, Grades 2–4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD *or pericardiocentesis* as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, *antipyretic medications*, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-L1 or PD-1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table 5.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator′s judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 5 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, *antipyretic medications*, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact *the* Medical Monitor.

Table 5 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 5 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; IV = intravenous; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: These management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and who then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic *medications*, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based *on the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic *medication*, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 6.

Table 6 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as Grade 3.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

Table 6 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based *on the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's *benefit-risk* assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 7.

Table 7 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 7 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Stevens Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in *Table 8 , with specific guidelines for myelitis provided in Table 9* .

Table 8 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab* [b] – *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated)*f* to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 9 Management *Guidelines for Immune-Mediated Myelitis*

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b]

	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor*[c]

Table 12 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's benefit–risk* assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly

- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
  - Platelet count $<100\times10^9$/L ($<$100,000/μL)
  - ANC $<1.0\times10^9$/L ($<$1000/μL)
- Fasting triglycerides >2.992 mmol/L ($>$265 mg/dL) and/or fibrinogen <1.5 g/L ($<$150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L ($>$500 ng/mL)
- Soluble IL–2 receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L ($>$684 ng/mL)
- At least two of the following:
  - Platelet count $\leq181\times10^9$/L ($\leq$181,000/μL)
  - AST ≥48 U/L
  - Triglycerides >1.761 mmol/L ($>$156 mg/dL)
  - Fibrinogen ≤3.6 g/L ($\leq$360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; IV = intravenous; MAS = macrophage activation syndrome.

REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology

International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Appendix 20
Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

The following adverse events are potential overlapping toxicities associated with combination use of trastuzumab emtansine and atezolizumab: pulmonary and hepatic events.

If trastuzumab emtansine is held for toxicity, then atezolizumab/placebo must also be held. If trastuzumab emtansine is discontinued, atezolizumab/placebo must also be discontinued. The Medical Monitor is available to the investigator to consult and answer any questions about assigning causality of the toxicity.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and trastuzumab emtansine.

Mild to moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (diffusion capacity of the lung for carbon monoxide)
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study, and will also have CT scans of the chest at every tumor assessment. See Table 1 for management guidelines for interstitial lung disease and pneumonitis. See Appendix 19 for atezolizumab guidelines for all other pulmonary events.

In this study, atezolizumab *is to be* discontinued for all grades of interstitial lung disease and pneumonitis.

Table 1 Management Guidelines for Interstitial Lung Disease and Pneumonitis

Severity	Trastuzumab Emtansine	Atezolizumab
Grade 1	*Withhold trastuzumab emtansine treatment until resolved to Grade 0* If resolved within 42 days, treat at the same dose level. If not resolved within 42 days, discontinue trastuzumab emtansine treatment.	Discontinue atezolizumab treatment.
Grade 2	*Withhold trastuzumab emtansine treatment* *If resolved to Grade 0 within 42 days, treat with one dose level reduction* *If not resolved within 42 days, discontinue trastuzumab emtansine treatment and contact Medical Monitor.*[b]	*Discontinue atezolizumab treatment.*
Grade 3 – 4	*Discontinue trastuzumab emtansine treatment.*	*Discontinue atezolizumab treatment.*

- [a] *Monitor and closely follow up in 2–7 days for onset of clinical symptoms and pulse oximetry (resting and ambulation). Consider follow-up imaging with Chest CT in 1-□2 weeks (or as clinically indicated)*

[b] *The Medical Monitor is available to advise as needed.*

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Liver function will be monitored throughout study treatment.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

If outcome of LFTs is worsening, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for worsening outcome of LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver

kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered. See Table 2 for management guidelines for atezolizumab and trastuzumab emtansine hepatic events.

See Table 2 for Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events. See Table 3 for dose modifications of trastuzumab emtansine for hyperbilirubinemia.

Note: No dose modification for atezolizumab/placebo is indicated on the basis of hyperbilirubinemia alone.

Table 2 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Severity	Trastuzumab Emtansine	Atezolizumab/Placebo
ALT or AST increase that meets Hy's law criteria: ALT or AST $>3\times$ ULN in combination with TBILI $>2\times$ ULN or clinical jaundice	Discontinue trastuzumab emtansine treatment.	Discontinue atezolizumab/placebo treatment.
ALT or AST increase that does not meet Hy's law criteria ALT/AST Grade 1 ($>$ 1-0–3.0 $\times$ ULN)	Continue with the trastuzumab emtansine without dose modification and monitor LFTs.	Treat at the same dose level. Continue LFT monitoring.
ALT/AST Grade 2 (>3.0–$5.0\times$ ULN)	Treat at the same dose level.	Withhold atezolizumab/placebo dose. If persists >5–7 days: Intiate 1–2 mg/kg/day prednisone or equivalent per day; when recover to Grade ≤ 1, taper steroids over ≥ 1 month. Resume therapy when systemic steroid dose is $\leq$ 10mg oral prednisone equivalent per day and resume when recovery to Grade ≤ 1 at same dose within 12 weeks. Permanently discontinue atezolizumab/placebo and contact the Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.

Table 2 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Trastuzumab Emtansine	Atezolizumab/Placebo
ALT/AST Grade 3 (> 5.0–20.0 × ULN)	Withhold trastuzumab emtansine dose. Do not administer trastuzumab emtansine until recovery to Grade ≤ 2, and then resume with dose reduction by one level. Discontinue trastuzumab emtansine treatment if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.	Discontinue atezolizumab/placebo dose. Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary. Start corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1. Contact the Medical Monitor if atezolizumab/placebo treatment is discontinued.
ALT/AST Grade 4 (> 20.0 × ULN)	Discontinue trastuzumab emtansine treatment. Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.	Discontinue atezolizumab/placebo treatment. Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary. Start corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1. Contact the Medical Monitor if atezolizumab/placebo treatment is discontinued.

Table 2 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Trastuzumab Emtansine	Atezolizumab/Placebo
NRH If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered.	Discontinue all study treatment and have the patient evaluated by a hepatologist.	Discontinue all study treatment and have the patient evaluated by a hepatologist

GI = gastrointestinal; LFT = liver function test; MBC = metastatic breast cancer; NRH = Nodular Regenerative Hyperplasia; TNF = tumor necrosis factor; ULN = upper limit of normal.

Table 3 Trastuzumab Emtansine Dose Modification Guidelines for Hyperbilirubinemia in Patients with Metastatic Breast Cancer

Severity	Action to be Taken
Grade 2 (> 1.5 to $\leq 3 \times$ ULN)	Withhold trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 and then resume at the same dose level.
Grade 3 (> 3 to $\leq 10 \times$ ULN)	Withhold trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1 and then resume by one dose level reduction.
Grade 4 ($> 10 \times$ ULN)	Discontinue trastuzumab emtansine treatment.

ULN = upper limit of normal.

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