

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

NCT Number: NCT02924883

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PROTOCOL

TITLE: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR ATEZOLIZUMAB-PLACEBO IN PATIENTS WITH HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB AND TAXANE BASED THERAPY

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TEST PRODUCT: Trastuzumab Emtansine (RO5304020)
Atezolizumab (RO5541267)

MEDICAL MONITOR: [REDACTED], M.D.
[REDACTED], Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 14 April 2016

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Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[REDACTED]	Company Signatory	09-Aug-2017 16:54:13

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- The following changes to the study design have been made given the emerging scientific understanding of delayed therapeutic effects with immunotherapy agents and the need for more mature progression-free survival (PFS) and overall survival (OS) data to gauge efficacy:
 - The interim analysis for PFS has been removed (Sections 6.4.1 and 6.9).
 - The number of PFS events for the primary PFS analysis has been increased from 95 to 115 (Sections 3.2, 6.1, and 6.4.1).
- The first analysis of OS will be performed at the time of the primary PFS analysis. Another update for OS will be performed at approximately 12 months after the primary PFS analysis. The final OS analysis will be performed at approximately 24 months after the primary PFS analysis or when ~50% OS events from 200 patients can be obtained, whichever occurs first. The Sponsor may consider additional OS updates beyond 24 months after primary PFS analysis if more mature OS data are requested by the Health Authority. The changes allow for a better understanding of the therapeutic effects of the experimental treatment on OS and provide more mature data for benefit-risk assessment with the additional follow-up period for survival data (Section 6.4.2).
- The assumed median PFS time for the control arm, trastuzumab emtansine plus placebo, has been changed from 9.6 months (observed in EMILIA study) to 6.2 months (observed in TH3RESA study) to reflect the observed prior treatment demographics of patients enrolled in the study (Section 6.1).
- The estimated time for primary PFS analysis has been changed from approximately 19–21 months after first patient enrolled to approximately 15–17 months after first patient enrolled, due to the updated assumption of median PFS time for the control arm and the updated number of events for primary PFS analysis (Sections 3.2 and 6.4.2).
- The pregnancy reporting process has been clarified (Sections 5.4.3.1 and 5.4.3.2).
- The safety risks for trastuzumab emtansine and atezolizumab have been updated, in line with the respective Investigator's Brochure updates (Sections 5.1.1.5 and 5.1.2, respectively).
- Brain assessment has been clarified (Section 4.5.5).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (Section 5.3.5.8).
- Event reporting for hospitalization has been clarified (Section 5.3.5.11).
- Brain computed tomography (CT)/ magnetic resonance imaging (MRI) requirements have been clarified (Sections 4.5.5 and Appendix 1)

- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).

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.

PROTOCOL AMENDMENT, VERSION 3: SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor for the study has been changed from [REDACTED] M.D., Ph.D. to [REDACTED] M.D.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.4: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The safety and tolerability of the combination of trastuzumab emtansine and atezolizumab is currently unknown and is being evaluated in an ongoing, Phase Ib study (Study GO29831); *Section 1.3.4*); whilst no dose-limiting toxicities have been observed in the the safety cohort of 6 patients treated with trastuzumab emtansine+atezolizumab, there remains the potential for unknown and overlapping toxicity. To minimize this risk, stringent inclusion and exclusion criteria (Section 4.1), close safety monitoring (Section 5.3) together with rules for dose modifications and safety management guidelines for known risks of single-agent trastuzumab emtansine and atezolizumab have been implemented in the current study. Furthermore, guidance on management of potential overlapping toxicities is described in Section 5.1.4. An independent Data Monitoring Committee (iDMC) (Section 5.1) has also been incorporated into the trial design to periodically review aggregate safety data (refer to the iDMC Charter for a detailed monitoring plan).

SECTION 2.1.1: Primary Efficacy Objective

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

SECTION 2.1.2: Secondary Efficacy Objectives

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

SECTION 2.1.3: Exploratory Efficacy Objectives

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

SECTION 3.1: DESCRIPTION OF THE STUDY

Patients will be treated in one of the following arms:

- **Arm B:** trastuzumab emtansine 3.6 mg/kg and atezolizumab/~~placebo~~ 1200 mg, q3w (approximately 133 patients)

In patients who continue treatment beyond radiographic disease progression per RECIST v1.1, tumor response will also continue to be assessed using immune-modified RECIST criteria (Appendix 5) every 6 weeks (± 7 days) until study treatment discontinuation. Immune-modified RECIST criteria *may* account for the possibility of delayed anti-tumor activity that may be preceded by initial apparent radiological progression, including the appearance of new lesions.

SECTION 3.2: END OF STUDY AND LENGTH OF STUDY

This study is anticipated to have a recruitment period of approximately 9 months. The final analysis of the primary efficacy endpoint will be conducted when approximately ~~95~~115 PFS events have occurred, based on investigator assessments. This is assumed to be approximately ~~20-15-17~~ months after the enrollment of the first patient (FPI).

The end of study is triggered by the final OS analysis following last patient last visit (LPLV) ~~which~~*that* is planned to occur approximately ~~9-24~~ months after the primary efficacy analysis *or at approximately 50% OS events from 200 patients can be obtained, whichever occurs first. The Sponsor may consider additional OS update(s) beyond 24 months after primary PFS analysis if more mature OS data are requested by the Health Authority.* The Sponsor may also terminate the study at any time.

The total duration of the study is expected to be approximately ~~29-40~~ months.

SECTION 3.3.6: Rationale for Collection of PK and ATA Samples

Both atezolizumab and trastuzumab emtansine single-agent pharmacokinetics have been characterized in multiple Phase I, II, and III studies. Refer to the latest versions of the Trastuzumab Emtansine and Atezolizumab IBs for further details. In this study, PK/ATA samples will be collected from all patients in both Arm A and Arm B as detailed in Appendix 2. Sparse sampling will be used in this study. PK and immunogenicity of atezolizumab (Arm B-A) and trastuzumab emtansine (Arm A and Arm B) will be assessed...

SECTION 4.2.2: Stratification

Randomization will be stratified based on the following ~~two~~*three* factors:

SECTION 4.3.5: Post-Trial Access to Trastuzumab Emtansine and Atezolizumab

The Sponsor will evaluate the appropriateness of continuing to provide trastuzumab emtansine and atezolizumab (where applicable) to patients on protocol treatment at the end of the study ~~as defined in~~*(see Section 3.2)- in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:*

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

SECTION 4.5.5: Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of the following assessments every 6 weeks: 1) CT and/or MRI of the chest/abdomen/pelvis, as well as other known sites of disease, *including brain*, 2) If a patient has only bone as a site of involvement at screening which is determined to be measurable disease as per RECIST 1.1, then a bone scan or PET scan is mandated at every tumor assessment, ~~or~~ otherwise, a bone scan or PET scan is to be performed as clinically indicated, e.g., suspicion of disease progression, 3) in cases where patients demonstrate control of their systemic disease but who newly develop isolated brain metastases and are eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments, *and* 4) any other imaging studies felt to be clinically indicated by the treating physician.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if PD is suspected. If the initial screening bone scan or PET scan indicates bone metastases and this is the only site of involvement and is determined to be measurable disease per RECIST 1.1, then a bone scan or PET scan needs to be performed every 6 weeks. If the screening scan shows evidence of either non-measurable bone metastases or no bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion. ~~Similarly, If the brain is not identified as a site of involvement at screening, then brain~~ CT or MRI only needs to be repeated beyond screening, if clinically indicated. In cases where a patient demonstrates control of their systemic disease but who newly develops isolated brain metastases and is eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments (Section 3.1).

SECTION 5.1.1.5: Hematologic Toxicity

~~Cases of bleeding events with a fatal outcome have been observed. Severe cases of hemorrhagic events, including central nervous system hemorrhage, have been reported in clinical trials of trastuzumab emtansine; these events were independent of ethnicity. In some of the observed cases, the patients were also receiving anti-coagulation therapy.~~

Patients with thrombocytopenia ($\leq 100,000/\text{mm}^3$) and patients on anti-coagulant treatment should be monitored closely during treatment with trastuzumab emtansine. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Trastuzumab emtansine has not been studied in patients with platelet counts $\leq 100,000/\text{mm}^3$ prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater ($< 50,000/\text{mm}^3$), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq 75,000/\text{mm}^3$).

SECTION 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 other cases, 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.

SECTION 5.1.2: Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such atezolizumab therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. To date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, myocarditis, hypophysitis, and meningoencephalitis. *In addition, systemic immune activation (described below) is a potential risk when atezolizumab is given in combination with other immunomodulating agents. For further details regarding the up-to-date clinical safety of atezolizumab, see the most recent version of the Atezolizumab IB.*

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- *CBC with peripheral smear*
- *PT, PTT, fibrinogen, and D-dimer*
- *Ferritin*
- *Triglycerides*
- *AST, ALT, and total bilirubin*
- *LDH*
- *Complete neurologic and abdominal examination (assess for hepatosplenomegaly)*

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

SECTION 5.1.3.2.1: Cardiotoxicity

The decision to stop or continue trastuzumab emtansine treatment should be on the basis of the algorithm shown in Figure 3 *for 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)...

SECTION 5.1.3.3: Management of Patients Who Have Atezolizumab/Placebo Related Specific Adverse Events

Guidelines for the management of patients who experience specific adverse events (other than systemic immune activation) are provided in the most recent version of the Atezolizumab IB.

No dose modification for atezolizumab is allowed.

SECTION 5.3.5.8: Deaths

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. ~~The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ 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").*

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

~~The following hospitalization scenarios are not considered to be adverse events:~~

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

~~The following hospitalization scenarios are~~ *An event that leads to hospitalization under the following circumstances is not considered to be serious adverse events, but should be reported as adverse events instead:*

SECTION 5.4.1: Emergency Medical Contacts Medical Monitor Contact Information

Medical Monitor [REDACTED] M.D., Ph.D.

Telephone No.:

[REDACTED]

Mobile Telephone No.:

[REDACTED]

SECTION 5.4.3.1: Pregnancies in Female Patients

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 serious adverse events 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. Additional information on any atezolizumab/placebo or trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). 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.

~~A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated by the EDC system and will be sent to Roche Safety Risk Management. Additional information on any atezolizumab/placebo or trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report during the first trimester at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should immediately and permanently discontinue the study drug 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 serious adverse events 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 the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting 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 pregnancy), 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 again, all information will need to be entered and submitted via the EDC system.~~

SECTION 5.4.3.2: Pregnancies in Female Partners of Male Patients

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. 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 drug. When permitted by the site, the pregnant partner would need to sign an Authorization for 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 when updated information on the course and outcome of the pregnancy becomes available. Additional information on any atezolizumab/placebo or trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). 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.

~~A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Additional information on any atezolizumab/placebo or trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report during the first trimester at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). 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 drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. 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.~~

~~In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.~~

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint for this study is PFS based on investigator tumor assessment. *The primary PFS analysis will be performed when approximately 115 PFS events have occurred.*~~The timing of the primary efficacy analysis will be event driven.~~

With approximately 200 patients randomized according to a 2:1 randomization (approximately 133-67 patients will be randomized to Arm A and approximately 67-133 patients will be randomized to Arm B) the study has the estimated power for the PFS HRs presented in Table 14.

The above study design considerations assume proportional hazards, a cumulative dropout rate of 10% in each treatment arm and result in an estimated recruitment time of about 9 months (with ramp up in the first 4 months). The estimated time from FPI to final primary PFS analysis is 19 to 24-15 to 17 months, depending on PFS HR assumption.

SECTION 6.4.1: Primary Efficacy Endpoint

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

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 Section 4.2.2 (excluding liver metastases), will be used to compare PFS between the treatment arms at the overall two-sided significance level of 5%. Liver metastases will be excluded because of the potential that some of the strata may have very few patients, which would result in a loss of power. The stratification factors will be based on data collected by the IxRS rather than on data collected on the eCRFs. The unstratified log-rank test result will also be provided. The Cox proportional hazards model, stratified by the previous noted stratification factors, excluding liver metastases, will be used to estimate the HR and to calculate the 95% CI of the HR.

~~The Kaplan-Meier method will be used to estimate median PFS for each treatment arm. The 2-sided log-rank test, stratified by world region (Western Europe vs U.S. vs Rest of World) and PD-L1 status (IC 0 vs IC 1-3) will be used to compare PFS between the treatment arms. The unstratified log-rank test result will also be provided. The stratified Cox regression model will be used to estimate the HR and to calculate the 95% CI of the HR.~~

~~A group sequential design will be used for testing the primary efficacy endpoint PFS to account for the conduct of interim analyses. An alpha spending using a gamma function with parameter 1 will be utilized to control the overall Type I error rate. The interim PFS analysis will be conducted when approximately 63 investigator-assessed PFS events (66.7% information fraction) have been observed and is anticipated to occur approximately 14 months from FPI. Key design characteristics of the interim PFS analysis are detailed in Table 15.~~

Table 15 — PFS Interim Analysis Design Characteristics using Gamma (-1) Alpha Spending Function

Number of PFS Events	Information Fraction	Cumulative Alpha Spent	Crossing Boundary in HR	Crossing Boundary in P-Value
63	66.7%	0.028	HR \leq 0.574	p \leq 0.014

HR=hazard ratio; PFS=progression free survival.

~~The sponsor may decide to consider adding an additional interim analysis including efficacy data which will be pre-specified in the SAP as appropriate.~~

~~The interim analyses will be conducted by an iDMC with the support of an independent Data Coordinating Center (iDCC). Interactions between the iDMC and the sponsor will follow the iDMC charter. The decision to conduct the interim analysis, rationale, timing, and statistical details will be documented in the SAP. Additional interim analyses may be conducted if requested by health authorities. The *primary* final PFS analysis will be performed when approximately 95-115 investigator-assessed PFS events have been observed and is anticipated to occur approximately 19 to 24-15 to 17 months from FPI, depending on PFS HR assumptions (Section 6.1).~~

SECTION 6.4.2: Secondary Efficacy Endpoints

Overall Survival

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

Objective Response Rate

Objective response, defined as a CR or PR, will be determined by investigator tumor assessment using RECIST 1.1. *Only patients with measurable disease at baseline will be included in the analysis of objective response.* Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified according to the factors specified in Section 4.2.2 (*excluding liver metastases*) will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

~~PFS in Subgroups of Patients Defined as PD-L1Dx+ and PD-L1Dx~~

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

SECTION 6.4.3: Exploratory Efficacy Endpoints **Objective Response Rate based on Immune Modified RECIST**

Objective response, defined as a complete response (CR) or partial response (PR), will be determined by investigator tumor assessment using immune-modified RECIST. Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified according to the factors specified in Section 4.2.2 (*excluding liver metastases*) will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

Duration of Response based on Immune-Modified RECIST

[Note: title change only]

SECTION 6.5: SAFETY ANALYSES

Adverse Events

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

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

- *Sponsor-defined adverse events of special interest*

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

Additional *safety* analyses may be performed as indicated.

SECTION 6.9.1: Planned Interim Analysis

There is no planned interim efficacy analysis for PFS.

~~An interim efficacy analysis is planned for the primary efficacy endpoint PFS when approximately 63 investigator-assessed PFS events have been observed, anticipated to occur around 14 months after FPI. An alpha spending using a gamma function with parameter 1 will be utilized to control the overall Type I error rate for PFS. Further details are given in Section 6.4.1.~~

~~The sponsor may decide to consider adding an additional interim analysis including efficacy data which will be pre-specified in the SAP as appropriate.~~

~~The interim analyses will be conducted by an iDMC with the support of an independent iDCC. Interactions between the iDMC and the sponsor will follow the iDMC charter. The decision to conduct the interim analysis, rationale, timing, and statistical details will be documented in the SAP. Additional interim analyses may be conducted if requested by health authorities.~~

SECTION 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.*

SECTION 9.4: ADMINISTRATIVE STRUCTURE

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 patient safety data in unblinded fashion during course of the study, ~~as well as conducting efficacy interim analyses as specified in the SAP.~~ 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.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

FIGURE 3: Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Treatment Based on LVEF Assessments in Patients

Figure 3 has been revised to reflect changes in the protocol.

TABLE 10: Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Table 10 has been revised to reflect most recent version of Investigator's Brochure.

TABLE 14: Estimated Power at *Primary* ~~Final~~ PFS Analysis for Different PFS HRs

Table 12 has been revised to reflect changes in the protocol.

TABLE 15: PFS Interim Analysis Design Characteristics using Gamma (-1) Alpha Spending Function

Table 15 has been deleted.

APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR ATEZOLIZUMAB-PLACEBO IN PATIENTS WITH HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB AND TAXANE BASED THERAPY

PROTOCOL NUMBER: WO30085

VERSION NUMBER: 3

EUDRACT NUMBER: 2015-004189-27

IND NUMBER: 71,072

TEST PRODUCT: Trastuzumab Emtansine (RO5304020)
Atezolizumab (RO5541267)

MEDICAL MONITOR: [REDACTED] M.D.
[REDACTED] Ph.D.

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

PROTOCOL SYNOPSIS

TITLE: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR ATEZOLIZUMAB-PLACEBO IN PATIENTS WITH HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB AND TAXANE BASED THERAPY

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IND NUMBER: 71,072

TEST PRODUCT: Trastuzumab Emtansine (RO5304020)
Atezolizumab (RO5541267)

PHASE: Phase II

INDICATION: Locally advanced or metastatic breast cancer

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

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

Primary Efficacy Objective

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

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

Secondary Efficacy Objective

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

- Overall survival (OS), defined as the time from randomization to death from any cause
- Objective response, defined as a complete response (CR) or partial response (PR) on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Duration of objective response, defined as the time from first occurrence of a documented objective response to disease progression, as determined by investigator assessment using RECIST v1.1 or death from any cause, whichever occurs first

Exploratory Efficacy Objective

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

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

Safety Objective

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

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

Pharmacokinetic Objective

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

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

Immunogenicity Objective

The secondary immunogenicity objectives for this study are:

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

The exploratory immunogenicity objectives for this study are as follows:

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

Biomarker Objective

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

Study Design

Description of Study

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

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

Patients will be treated in one of the following arms:

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

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

Number of Patients

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

Target Population

Inclusion Criteria

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

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

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

Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

- HER2-positive breast cancer (BC) as defined by an immunohistochemistry (IHC) score of 3+ or gene amplified by in situ hybridization (ISH) as defined by a ratio of \geq 2.0 for the number of HER2 gene copies to the number of chromosome 17 copies, prospectively tested by a Sponsor- designated central laboratory prior to enrollment. Both IHC and ISH assays will be performed; however, only one positive result is required for eligibility.

If multiple tumor specimens are submitted, the HER2 IHC score and or ISH amplification ratio will first be assessed on the archival specimen for the purpose of determining

eligibility. For patients with bilateral BC, HER2 positivity must be demonstrated in both locations for archival tissue or in a metastatic biopsy.

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

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

- Histologically or cytologically confirmed invasive BC: incurable, unresectable, locally advanced BC previously treated with multimodality therapy or MBC.
- Prior treatment for BC in the: adjuvant; unresectable locally advanced; or metastatic settings; which must include both, a taxane and trastuzumab (alone or in combination with another agent)
- Progression must have occurred during or after most recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy.
- Patients must have measurable disease that is evaluable per RECIST 1.1.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):
 - Absolute neutrophil count ≥ 1500 cells/ μL (without granulocyte-colony stimulating factor [support] within 7 days prior to Cycle 1, Day 1
 - Platelet count $\geq 100,000/\mu\text{L}$ (without transfusion within 7 days prior to Cycle 1, Day 1)
 - Hemoglobin ≥ 9.0 g/dL
 - Patients may be transfused or receive erythropoietic treatment to meet this criterion.
 - Albumin > 2.5 g/dL
 - AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ the upper limit of normal (ULN) with the following exceptions:
 - Patients with documented bone metastases: alkaline phosphatase $\leq 5 \times$ the ULN
 - Total bilirubin $\leq 1.5 \times$ the ULN
 - INR and aPTT $\leq 1.5 \times$ the ULN
 - This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
 - Calculated creatinine clearance ≥ 30 mL/min
- Negative serum pregnancy test within 7 days of enrollment for pre-menopausal women and for women less than 12 months after the onset of menopause.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine, or 5 months after the last dose of atezolizumab/placebo, whichever is later.

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

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

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
 - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 7 months after the last dose trastuzumab emtansine. Men must refrain from donating sperm during this same period.
 - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine to avoid exposing the embryo.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Prior treatment with trastuzumab emtansine, CD137 agonists, anti-programmed death-1 (PD-1), or anti-PD-L1 therapeutic antibody or pathway-targeting agents.
- Receipt of any anti-cancer drug/biologic or investigational treatment 21 days prior to Cycle 1 Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1 Day 1; recovery of treatment-related toxicity consistent with other eligibility criteria.
- Radiation therapy within 2 weeks prior to Cycle 1, Day 1
 - The patient must have recovered from any resulting acute toxicity (to Grade \leq 1) prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines as specified below:
 - Doxorubicin > 500 mg/m²
 - Liposomal doxorubicin > 500 mg/m²
 - Epirubicin > 720 mg/m²
 - Mitoxantrone > 120 mg/m²
 - Idarubicin > 90 mg/m²
 - If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m² doxorubicin.
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence.
- Cardiopulmonary dysfunction as defined by:
 - Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg)
 - Inadequate left ventricular ejection function at baseline, < 50% by either ECHO or MUGA
 - History of symptomatic congestive heart failure (CHF)-Grade \geq 3 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or Class \geq II New York Health Association
 - History of a decrease in left ventricular ejection function to < 40% or symptomatic CHF with prior trastuzumab treatment
 - Myocardial infarction or unstable angina within 6 months of randomization
 - Current dyspnoea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
 - Serious cardiac arrhythmia not controlled by adequate medication
- Patients with severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures).
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment.
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis or active infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)
 - Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or HCV antibody. HIV, HBV, or HCV assessments are required at screening.
 - Patients who test positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV DNA.
 - Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.
- Need for current chronic corticosteroid therapy (≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)
 - Stable use (i.e., no change in dose within 3 months prior to Cycle 1, Day 1) of inhaled corticosteroids is allowed.
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization.
- Patients with known central nervous system (CNS) disease are not eligible, except for treated asymptomatic CNS metastases, provided that all of the following criteria are met:
 - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
 - No ongoing requirement for corticosteroids as therapy for CNS disease
 - No stereotactic radiation within 14 days prior to randomization
 - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
- Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Leptomeningeal disease
- Symptomatic pleural effusion, pericardial effusion, or ascites.
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.
 - Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.
 - Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade ≥ 3 peripheral neuropathy (according to the NCI CTCAE v4.0).
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins.

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

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

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

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

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

Rash must cover < 10% of body surface area.

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

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

Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.

- Prior allogeneic stem cell or solid organ transplantation.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography scan.

Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.

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

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

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

Stable use (i.e., no change in dose within 3 months prior to Cycle 1, Day 1) of inhaled corticosteroids is allowed

- Breastfeeding, or intending to become pregnant during the study

End of Study

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

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

Length of Study

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

Investigational Medicinal Products

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

Test Product (Investigational Drug)

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

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

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

Both trastuzumab emtansine and atezolizumab/placebo should be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

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

Statistical Methods

Primary Efficacy Analysis

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

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

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

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

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

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

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

Secondary Efficacy Analysis

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

Overall Survival

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

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

Objective Response Rate

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

Duration of Response

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

Exploratory Efficacy Analysis

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

PFS Assessed in the PD-L1 Selected Subgroup

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

PFS Assessed Using Immune-Modified RECIST

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

Objective Response Rate based on Immune Modified RECIST

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

Duration of Response based on Immune-Modified RECIST

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

1-Year Survival Rate

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

Safety Analysis

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

Study Drug Exposure

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

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

Adverse Events

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

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

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

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

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

Deaths and causes of death will be summarized. Selected adverse events will be summarized by NCI CTCAE grade for each treatment arm based on pre-specified category definitions, including (but not limited to) hepatotoxicity, cardiac dysfunction, and thrombocytopenia.

In addition, adverse events occurring within 1 day (24 hours) of the first dose of each treatment cycle will be summarized to help characterize potential infusion-related reactions.

Additional *safety* analyses may be performed as indicated.

Laboratory Data

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

Pharmacokinetic Analysis

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

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

Additional PK and PD analyses will be conducted as appropriate.

Immunogenicity Analysis

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

Biomarker Analysis

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

Determination of Sample Size

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

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

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

Interim Analyses

There is no planned interim efficacy analysis for PFS.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADC	antibody–drug conjugate
anti-HBc	antibody to hepatitis B core antigen
ATA	anti-therapeutic antibody
BC	breast cancer
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome p450
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FPI	first patient enrolled
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IB	Investigator’s Brochure
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
ILD	interstitial lung disease
IL	interleukin
iDCC	independent Data Coordinating Center

Abbreviation	Definition
iDMC	independent data monitoring committee
IMP	investigational medicinal product
IND	Investigation New Drug Application
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intention-to-treat
IV	intravenous
IxRS	interactive Web or voice response system
LABC	locally advanced breast cancer
LFT	liver function test
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
<i>MRI</i>	<i>magnetic resonance imaging</i>
MUGA	multi-gated acquisition scan
NCI	National Cancer Institute
NGS	next-generation sequencing
NRH	nodular regenerative hyperplasia
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
<i>PET</i>	<i>positron emission tomography</i>
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response
q2w	every 2 weeks
q3w	every 3 weeks
RCC	renal cell carcinoma
RBR	Research Biosample Repository

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SIA	systemic immune activation
TC	tumor cell
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TPC	treatment of physician's choice
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WGS	whole genome sequencing

1. **BACKGROUND**

1.1 **BACKGROUND ON BREAST CANCER**

Breast cancer (BC) is the most common cancer among women in the world with an estimated 1.67 million cases diagnosed globally per year and a mortality rate of approximately 520,000 deaths ([Globocan 2012](#)). While advances in early diagnosis and adjuvant therapy have led to a decrease in mortality rates from BC in developed countries, the prevalence of metastatic breast cancer (MBC) is still high and it is not considered curable, with the main goals of treatment being to improve patients' quality of life and prolong survival ([Cardoso et al 2014](#)).

Human epidermal growth factor 2 (HER2), also known as erbB2, neu, and p185HER2, represents a prominent target in BC with approximately 15%–20% of patients with primary invasive BCs 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](#)).

Until recently, for patients with HER2-positive MBC, the combination of trastuzumab and a taxane was widely accepted as the first-line treatment option of choice 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 overall survival (OS) with a generally similar safety profile (Study WO20698/TOC4129g [[Baselga et al. 2012](#)]) and is the new standard of care in many countries.

In patients with HER2-positive advanced BC 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](#)]) or compared to a treatment of physicians' choice in patients who previously received trastuzumab, taxane and lapatinib ([Wilders 2015](#)). Trastuzumab emtansine is considered standard of care in many countries in the aforementioned patient population.

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 BC.

1.2 BACKGROUND ON TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (Kadcyla[®], trastuzumab emtansine is a novel 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. Data from clinical trials of trastuzumab emtansine that are relevant to the design of the current trial are summarized in Sections 1.2.1 and 1.2.2. Refer to the most recent version of the trastuzumab emtansine Investigator's Brochure (IB) for further information on all of the completed and ongoing trastuzumab emtansine studies.

1.2.1 Study TDM4370g/BO21977 (EMILIA)

Study TDM4370g/BO21977 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/m² 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+capecitabine arm, with a median duration of response (DOR) of 12.6 months versus 6.5 months, respectively.

Trastuzumab emtansine was well tolerated, with no unexpected safety signals at the time of the primary analysis. The most common Grade ≥ 3 adverse events in the trastuzumab emtansine arm were thrombocytopenia (12.9% vs. 0.2%, respectively), increased AST (4.3% vs. 0.8%), and increased ALT (2.9% vs. 1.4%); the most common Grade ≥ 3 adverse events in the lapatinib+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 adverse events in the trastuzumab emtansine arm was 40.8% versus 57.0% in the lapatinib+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+capecitabine, compared with 30.9 months in patients treated with trastuzumab emtansine.

The final descriptive OS analysis showed a consistent survival benefit for trastuzumab emtansine compared with lapatinib+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 ([Dieras et al 2015](#)).

1.2.2 Study TDM4997g/BO25734 (TH3RESA)

Study TDM4997g/BO25734 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<0.0001). 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 adverse events (32.3% vs. 43.5%). Grade ≥ 3 adverse events 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 2nd 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 ([Wildiers et al, 2015](#)).

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab, an engineered anti-programmed death–ligand 1 (PD-L1) antibody, is a humanized immunoglobulin G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function and depletion of cells expressing PD-L1 in humans.

PD-L1 is an extracellular protein, which down regulates immune responses primarily in peripheral tissues through binding to its two receptors: programmed death–1 (PD-1) and B7.1. Many human tumors overexpress PD-L1, which acts to suppress anti-tumor immunity. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer ([Blank et al. 2005](#); [Keir et al. 2008](#)). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production ([Butte et al. 2007](#); [Yang et al. 2011](#)). Overexpression of PD-L1 on TCs has been reported to impede anti-tumor immunity, resulting in immune evasion ([Blank and Mackensen 2007](#)). Therefore, interruption of the PD-L1/PD-1 and the PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1, and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

Atezolizumab was approved by the U.S. Food and Drug Administration (FDA) in May 2016 for the treatment of patients with locally advanced or mUC who 1) have disease progression during or following platinum-containing chemotherapy or 2) have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Additionally, atezolizumab was approved by the U.S. FDA in October 2016 for the treatment of patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Patients with epidermal growth factor receptor or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

Refer to the most recent version of the Atezolizumab IB for further details.

1.3.1 Study PCD4989g

Study PCD4989g is a Phase Ia, multicenter, first-in-human, open-label, dose-escalation study, evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion q3w to patients with LABC or metastatic solid malignancies or hematologic malignancies.

The safety data for atezolizumab have been derived mainly from the treatment of patients in Study PCD4989g. As of 11 May 2015, there were 558 safety-evaluable patients from the Phase Ia study. The median duration of treatment was 12.1 weeks (range: 0.0–71.4 weeks), and the median number of atezolizumab cycles administered was 5.0 (range: 1–19 cycles). To date, no maximum tolerated dose, dose-limiting toxicities, or clear dose-related trends in the incidence of adverse events have been determined.

Of the 558 treated patients in Study PCD4989g, 520 (93.2%) patients experienced an adverse event regardless of attribution to atezolizumab. Treatment-related adverse events (per investigator's assessment of causality) were reported in 376 patients (67.4%). The majority of these adverse events were Grade 1 or 2 in maximum severity on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

The most frequently observed adverse events ($\geq 10\%$ of patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema.

Grade 3 and 4 adverse events were reported in 239 patients (42.8%) of which 66 (11.8%) were considered related to study drug by the investigator. Grade 3 and 4 adverse events considered related included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma glutamyl transferase, decreased lymphocyte count, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia. Safety findings in the triple-negative breast cancer (TNBC) cohort of Study PCD4989g are consistent with the data observed in the overall study population.

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)-based responses (i.e., RECIST Version 1.1 responses), have been observed in patients with different tumor types, including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, bladder cancer, colorectal cancer (CRC), head and neck cancer, gastric cancer, BC (including TNBC), and sarcoma treated with atezolizumab monotherapy in Study PCD4989g.

Among 386 evaluable patients enrolled prior to 1 July 2013 (data cutoff of 1 January 2014) there were 47 patients with responses with a median DOR of 75.7 weeks (range: 11.7+ to 85.9+ weeks, where "+" denotes a censored value). The majority of these responses have been durable, with 72.3% (34 of 47 patients) of responses ongoing as of the clinical cutoff date.

Analyses of tumor-infiltrating immune cells (ICs) for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results from Study PCD4989g suggest that PD-L1 expression in ICs is likely to be associated with response to atezolizumab.

Refer to the most recent version of the Atezolizumab IB for updated details regarding clinical safety and efficacy.

1.3.2 Study GP28328

Study GP28328 is a Phase Ib study evaluating the safety and pharmacology of atezolizumab administered with bevacizumab and/or chemotherapy to patients with advanced solid tumors. Arm A is evaluating 1200 mg atezolizumab + bevacizumab administered q3w to patients with multiple solid tumor types, including separate expansion cohorts in CRC and RCC. Arm B is evaluating atezolizumab + bevacizumab and oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) administered every 2 weeks (q2w) to patients with multiple solid tumor types, including CRC and BC. Arms C, D, and E are evaluating atezolizumab administered q3w to chemotherapy-naive patients with NSCLC in combination with carboplatin + paclitaxel, carboplatin + pemetrexed, and

carboplatin + nab-paclitaxel, respectively. Arm F is evaluating atezolizumab administered q2w in combination with weekly nab-paclitaxel in patients with TNBC who have received ≤ 2 lines of prior therapy for metastatic disease.

The primary objective is to evaluate the safety and tolerability. Other endpoints include efficacy as per investigator review by use of RECIST v1.1 criteria (best overall response, ORR, DOR, PFS), pharmacokinetics, and biomarkers.

For the initial metastatic TNBC safety cohort (n=8), atezolizumab (800 mg) was administered q2w, and nab-paclitaxel (125 mg/m²) was given on a 3-week on, 1-week off schedule. In the serial biopsy metastatic TNBC cohort (n=24), patients received nab-paclitaxel only on Days 1 and 8 of Cycle 1; subsequently, patients received the planned study treatment as described above. nab-Paclitaxel was administered for at least 4 cycles in the absence of disease progression or unacceptable toxicity. Atezolizumab and nab-paclitaxel could be administered as long as patients were experiencing clinical benefit per investigator discretion. If nab-paclitaxel was discontinued due to toxicity, atezolizumab could be continued as monotherapy.

As of 1 September 2015, safety data from 32 TNBC patients in GP28328 indicate that the combination appears to be well tolerated and is consistent with the known risks of nab-paclitaxel and atezolizumab. Few patients (16%) experienced adverse events leading to discontinuation of nab-paclitaxel and no patients discontinued atezolizumab due to an adverse event. The most frequently reported adverse events (>20%) included fatigue, pyrexia, diarrhea, nausea, alopecia, peripheral neuropathy and peripheral sensory neuropathy, infection, decreased neutrophil count, anemia, and bone pain. The majority of immune-mediated adverse events were Grade 1 or 2, and included dermatological events (41%), peripheral neuropathy (22%), liver enzymes increased, thyroid dysfunction, and pneumonitis. There were no fatal adverse events due to study drug.

The study demonstrated that the combination decreased tumor size (ORR, including confirmed responses) in 41.7% of patients, (n=24; 95% CI: 22.1, 63.4) ([Adams et al. 2015](#)).

Refer to the most recent version of the Atezolizumab IB for updated details on clinical activity and safety in all patients, regardless of tumor type.

1.3.3 Study WO29522

Study WO29522 is an ongoing phase III multicenter, randomized, placebo-controlled study of atezolizumab (anti-PD-L1 antibody) in combination with nab-paclitaxel compared to placebo with nab-paclitaxel for patients with previously untreated metastatic triple-negative breast cancer. Up to 900 patients will receive either atezolizumab or placebo (840mg IV, q2w) in combination with nab-paclitaxel (100 mg/m², q2w) on a

3 week on/1 week off schedule. The co-primary endpoints of the study are PFS by independent review and OS.

1.3.4 Study GO29831

Study GO29831 is an ongoing Phase Ib open-label, two-arm study evaluating the safety and pharmacokinetics of atezolizumab (anti-PDL-1 antibody) in combination with trastuzumab emtansine or with trastuzumab and pertuzumab in patients with HER2-positive breast cancer. The primary objective for this study is to evaluate the safety and tolerability of combination treatment with atezolizumab, trastuzumab, and pertuzumab or atezolizumab and trastuzumab emtansine in patients with HER2-positive MBC or treatment-naïve patients with operable, or LABC, or inflammatory EBC.

Stage 1 of the study consists of a 3-week safety run-in period for patients with HER2-positive MBC.

- Safety Evaluation Cohort 1A: Patients in Cohort 1A will receive atezolizumab (1200 mg q3w) in combination with trastuzumab (8-mg/kg loading dose, followed by a 6-mg/kg maintenance dose q3w) and pertuzumab (840-mg loading dose, followed by a 420-mg maintenance dose q3w).
- Safety Evaluation Cohort 1B: Patients in Cohort 1B will receive atezolizumab (1200 mg q3w) in combination with trastuzumab emtansine (3.6 mg/kg q3w).
- Safety Evaluation Cohort 1F: Patients in Cohort 1F will receive atezolizumab (1200 mg q3w) in combination with trastuzumab (8-mg/kg loading dose, followed by a 6-mg/kg maintenance dose q3w), pertuzumab (840-mg loading dose, followed by a 420-mg maintenance dose q3w), and docetaxel (75mg/m² q3w).

After 6 patients in the safety evaluation cohort have been treated in Cohort 1B with atezolizumab/trastuzumab emtansine for at least one cycle without experiencing more than one dose-limiting toxicity, an atezolizumab/trastuzumab emtansine safety expansion Cohort 2C will begin enrolling patients with HER2-positive MBC who have received prior treatment with trastuzumab and a taxane chemotherapy and who have progressed during or after the most recent treatment for locally advanced unresectable/MBC or within 6 months after completing adjuvant therapy. Up to 14 patients will be enrolled in Cohort 2C in order to gain additional safety and exploratory clinical activity data to inform potential future investigations of atezolizumab/trastuzumab emtansine in this patient population. A further 14 patients (previously progressed on trastuzumab and pertuzumab) will be enrolled in Cohort 2D and receive atezolizumab (1200 mg q3w) in combination with trastuzumab (8-mg/kg loading dose, followed by a 6-mg/kg maintenance dose q3w) and pertuzumab (840-mg loading dose, followed by a 420-mg maintenance dose q3w).

Stage 2 of the study will further explore the combination regimens in the neoadjuvant setting.

Refer to the most recent version of the Atezolizumab IB 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 (Verma et al. 2012). It is currently unknown if the addition of atezolizumab will improve the efficacy outcomes observed with trastuzumab emtansine monotherapy. Furthermore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because radiographic PD does not necessarily reflect therapeutic failure (Section 3). Therefore patients in the current study will have the option to be treated beyond progression to account for pseudo progression or delayed response to the combination therapy thereby minimizing the risk of discontinuing treatment prematurely. Furthermore, the ongoing Phase Ib GO29831 study is evaluating the efficacy of trastuzumab emtansine in combination with atezolizumab by conventional RECIST 1.1 and immune-modified RECIST response criteria.

The safety of trastuzumab emtansine is well established having been evaluated in 1871 patients with BC in clinical studies. It is generally well tolerated with the most common adverse events being nausea, fatigue, and headache. Adverse events of particular relevance include thrombocytopenia, hemorrhage, hepatotoxicity (increases in serum transaminases and nodular regenerative hyperplasia [NRH] of liver), infusion-related reactions/hypersensitivity, cardiac dysfunction (left ventricular dysfunction), peripheral neuropathy, and pulmonary toxicity (interstitial lung disease). Atezolizumab, has also been generally well tolerated (refer to the most recent version of the Atezolizumab IB for more details); adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab. To date, the majority of these events have been manageable without requiring treatment discontinuation.

The safety and tolerability of the combination of trastuzumab emtansine and atezolizumab is currently unknown and is being evaluated in an ongoing, Phase Ib study (Study GO29831; Section 1.3.4) whilst no dose-limiting toxicities have been observed in the safety cohort of 6 patients treated with trastuzumab emtansine+atezolizumab, there remains the potential for unknown and overlapping toxicity. To minimize this risk, stringent inclusion and exclusion criteria (Section 4.1), close safety monitoring (Section 5.3) together with rules for dose modifications and safety management guidelines for known risks of single-agent trastuzumab emtansine and atezolizumab have been implemented in the current study. Furthermore, guidance on management of potential overlapping toxicities is described in Section 5.1.4. An independent Data Monitoring Committee (iDMC) (Section 5.1) has also been incorporated into the trial design to periodically review aggregate safety data (refer to the iDMC Charter for a detailed monitoring plan).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of trastuzumab emtansine in combination with atezolizumab or placebo (atezolizumab/placebo) in patients with HER2-positive, locally advanced or MBC, who have received prior trastuzumab and taxane based therapy, either alone or in combination, and/or who have progressed within 6 months after completing adjuvant therapy.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

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

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

2.1.2 Secondary Efficacy Objectives

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

- OS, defined as the time from randomization to death from any cause
- Objective response, defined as a complete response (CR) or partial response (PR) on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using RECIST v1.1
- Duration of objective response, defined as the time from first occurrence of a documented objective response to disease progression, as determined by investigator assessment using RECIST v1.1 or death from any cause, whichever occurs first

2.1.3 Exploratory Efficacy Objectives

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

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator assessment using RECIST v1.1 or death from any cause, whichever occurs first, in the PD-L1 selected subgroup of patients defined as having tumor immune infiltrating cell expression of IC 1/2/3, as assessed by immunohistochemistry (IHC)
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs first

- Objective response, defined as a CR or PR on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using immune-modified RECIST
- Duration of objective response, defined as the time from first occurrence of a documented objective response to disease progression, as determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs first
- 1-year survival rate

2.2 SAFETY OBJECTIVES

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

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

2.3 PHARMACOKINETIC OBJECTIVES

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

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

2.4 IMMUNOGENICITY OBJECTIVES

The secondary immunogenicity objectives for this study are:

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

The exploratory immunogenicity objectives for this study are as follows:

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

2.5 BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To assess if baseline PD-L1 expression is associated with efficacy
- To assess if baseline immune status is associated with efficacy
- To assess if baseline immune status together with HER2 expression level (mRNA, protein and/or gene copy number/ratio) are associated with efficacy

- To assess changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with atezolizumab in combination with trastuzumab emtansine
- To evaluate the relationship between tumor biomarkers and efficacy
- To identify candidate biomarkers that correlate with safety signals

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

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

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

Patients will be treated in one of the following arms:

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

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

Patients must have measurable disease at baseline that is evaluable per RECIST 1.1 ([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.

Tumor assessments will be conducted approximately every 6 weeks (\pm 7 days) from the date of randomization, until investigator-assessed PD per RECIST 1.1 or death, whichever occurs first, regardless of dose delays or dose interruptions and even if study treatment has been discontinued as a result of patient or physician choice or unacceptable toxicity. Tumor assessment scans will be collected prospectively by the Sponsor in the event that an independent review facility (IRF) will be utilized.

Patients may remain on study treatment until investigator-assessed disease progression, unmanageable toxicity, or study termination by the Sponsor.

Patients who demonstrate control of their systemic disease, defined as having received clinical benefit (CR or PR of any duration or stable disease ≥ 4 months per RECIST v1.1; [Appendix 4](#)) from study therapy, but who newly develop isolated brain metastases that are treatable (e.g., with surgery, radiation or gamma-knife) may continue with study treatment until they experience systemic progression of their disease or further progression in the brain or both, based on investigator assessment. Other requirements include the following:

- The patient cannot miss more than one cycle (i.e., the maximum allowed time window between study treatments is 42 days) for the treatment of their brain disease.
- The patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 to continue on study therapy.
- Brain magnetic resonance imaging (MRI) or computed tomography (CT) scans are performed along with regularly scheduled tumor assessments (every 6 weeks) in these instances.
- Every attempt should be made to discontinue corticosteroids within 2 weeks of the last day of radiation therapy.

Upon radiographic disease progression per RECIST v1.1, patients may optionally continue to receive trastuzumab emtansine with blinded atezolizumab or placebo, provided they meet the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating clinically significant progression of disease
- No decline in ECOG performance status that can be attributed to disease progression

Absence of tumor progression at critical anatomical sites (e.g., newly developed leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions (i.e., pain secondary to disease or unmanageable ascites, etc.), as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Patients should discontinue study therapy upon evidence of further progression, defined as at least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm or unequivocal worsening of non-target disease.

In patients who continue treatment beyond radiographic disease progression per RECIST v1.1, tumor response will also continue to be assessed using immune-modified

RECIST criteria ([Appendix 5](#)) every 6 weeks (± 7 days) until study treatment discontinuation. Immune-modified RECIST criteria *may* account for the possibility of delayed anti-tumor activity that may be preceded by initial apparent radiological progression, including the appearance of new lesions.

For estimation of PFS, ORR, and DOR, tumor response will be based on both RECIST v1.1 ([Appendix 4](#)) and immune-modified RECIST ([Appendix 5](#)).

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

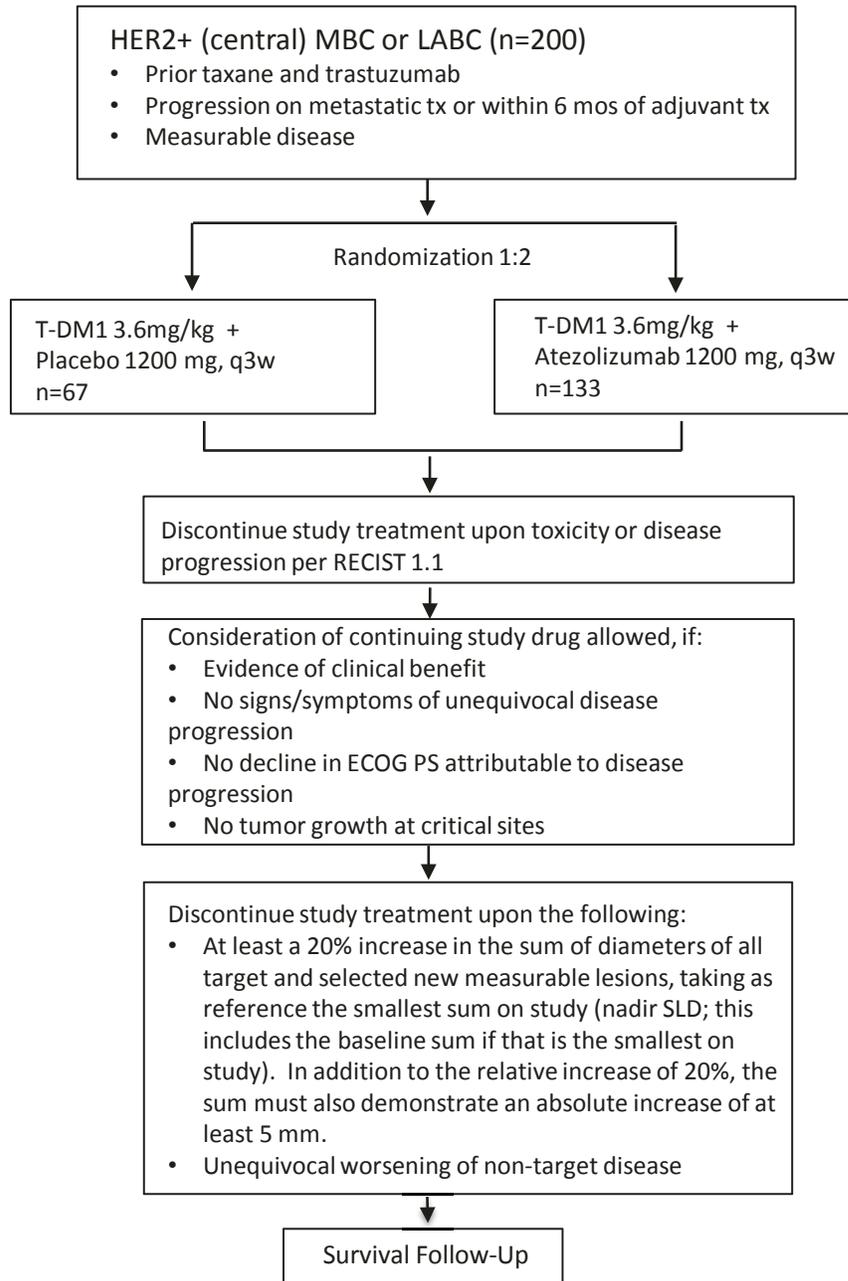
Serum samples will be collected to monitor pharmacokinetics and to detect presence of antibodies to trastuzumab emtansine and atezolizumab. Patient samples, including tumor tissues, as well as serum and plasma and whole blood, will be collected for exploratory biomarker assessments

After the Study Drug Completion Visit, all patients (regardless of reason for discontinuation) will be followed up for their survival status 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.

Patients who withdraw their consent from the study will be asked to participate in survival follow-up, where only information on the survival status of the patient will be collected. Patients willing to share their survival information will receive a separate and specific Informed Consent Form for this purpose.

A schedule of assessments is provided in [Appendix 1](#) and the study schema is in [Figure 1](#).

Figure 1 Study Schema



ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor; IV=intravenous; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; mos =months; PS=performance status; q3w=every 3 weeks; RECIST=response evaluation criteria in solid tumors; SLD=Sum of Longest Diameter; T-DM1=trastuzumab emtansine; tx=treatment.

Stratification factors: World region (W. Europe vs, U.S. vs. Rest of World). Tumor PD-L1 Status (IC 0 vs IC 1/2/3); Liver metastases (yes vs. no).

3.2 END OF STUDY AND LENGTH OF STUDY

This study is anticipated to have a recruitment period of approximately 9 months. The final analysis of the primary efficacy endpoint will be conducted when approximately 115 PFS events have occurred, based on investigator assessments. This is assumed to be approximately 15–17 months after the enrollment of the first patient (FPI).

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

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

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 and available clinical data from Study PCD4989g. Please refer to the most recent version of the Atezolizumab IB for further details.

3.3.2 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 + capecitabine in patients with HER2-positive MBC who were previously treated with trastuzumab and a taxane. An ongoing Phase Ib, GO29831 (cross-reference) will provide further information on the dose that is considered safe and tolerable to be combined with atezolizumab.

3.3.3 Rationale for Patient Population

Therapy with trastuzumab emtansine, has been demonstrated in a randomized study to improve PFS and OS compared to lapatinib + capecitabine, 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, MBC 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.

3.3.4 Rationale for Control Group

Based on the results from TDM4370g/BO21977 (Section 1.2.1), ([Verma et al. 2012](#)), trastuzumab emtansine has become widely accepted as the standard of care in patients who have been previously exposed to trastuzumab and or taxane; the patient population being studied in the current trial ([National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. 2014](#) and [Cardoso et al. 2014](#)).

The control arm will be used to ascertain the individual contribution of atezolizumab to efficacy with trastuzumab emtansine.

3.3.5 Rationale for Biomarker Assessments

Published results suggest that PD-L1 expression on TCs or ICs is associated with OS, PFS, and ORR in patients with advanced NSCLC treated with atezolizumab ([Spigel et al. 2015](#) and [Spira et al. 2015](#)). Increased response was also observed in patients with urothelial carcinoma in patients with increased levels of PD-L1 expression on immune cells ([Rosenberg et al. 2016](#)). This correlation was also observed in patients with various advanced incurable cancer types who were treated with atezolizumab ([Herbst et al, 2014](#)).

The contribution of the immune system to pathologic complete response in the breast (pCR) after neoadjuvant docetaxel with trastuzumab, pertuzumab, or both, or monoclonal antibodies alone has been explored in Study WO20697 ([Bianchini et al. 2015](#)). Tumor-infiltrating lymphocytes as a continuous variable and PD-L1 protein expression assessed as single marker were not significantly associated with pCR; However expression of some immune genes/metagenes showed association with pCR, e.g., lower levels of MHC1 and CTLA4 showed higher benefit from THP. The prognostic value of PD-L1 expression remains unclear in HER2-positive BC.

This study will evaluate the potential predictive value of PD-L1 expression for treatment of HER2-positive MBC with atezolizumab and trastuzumab emtansine. In addition, other exploratory biomarkers, such as potential predictive and prognostic markers that are related to PD-L1 activity, tumor immunobiology, mechanisms of resistance or tumor type may also be analyzed if supported by either nonclinical or clinical data.

Recently published data by Rosenberg et al. ([2016](#)) in a study with patients with urothelial cancer treated with atezolizumab shows the importance of genomic, molecular and immunological factors in addition to PD-L1 expression on immune cells in understanding response to atezolizumab.

Activating PIK3CA mutations in tumors have been evaluated as a resistance marker for HER2 targeted therapies in prior trials. In metastatic HER2-positive BC, (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 will be measured in baseline tumor tissue to confirm the finding from Study TDM4370g/BO21977.

Muller et al. (2015) demonstrated that trastuzumab emtansine increases tumor infiltrating lymphocytes (TILs) in human primary BC 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) recently 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 and on-treatment biopsies 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, including, but not limited to, cytokines such as interleukin (IL)-18 in blood samples.

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.

3.3.5.1 Rationale for Collection of Archival and Metastatic Tumor Specimens

If more than 1 formalin-fixed paraffin-embedded (FFPE) block exists from different time points e.g., initial diagnosis versus metastatic disease tissue, the most recently obtained block is mandatory to be sent and will be used for HER2 and PD-L1 analysis. If the FFPE block from the earlier time point is available, then this would be requested to also be sent to enable evaluation of the impact of prior therapies on the expression pattern of PD-L1. In addition to the assessment of PD-L1 status, other exploratory biomarkers such as potential predictive and prognostic markers related to the clinical benefit of trastuzumab emtansine plus atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be evaluated. These analyses may cover assessment of broad panels of genes (on both RNA and DNA level) that may contribute to the identification of biomarker signatures that are predictive of response to the combination of atezolizumab and trastuzumab emtansine.

HER2 status may be assessed on these paired samples as well to understand if HER2 status changes as a result of prior therapies.

3.3.5.2 Rationale for Collection of Optional Pre-treatment and Cycle 2 Biopsies

As described in Section 3.3.5.1, the collection of serial tissue biopsies from patients undergoing study treatment will contribute to the biologic understanding of how this combination therapy works and may lead to the identification of novel biomarker(s) and or biomarker signatures that are predictive of which types of tumors benefit most from the combination of trastuzumab emtansine and atezolizumab treatment. Additionally, these samples will give further insights in the early mechanisms of resistance and aid in the development of therapies to improve anti-tumor (immune) response.

The biomarkers and biomarker panels in the tumor during treatment should ideally be compared to the baseline biomarker level(s) at the time study treatment was started. Tumor tissue collected from patients is however often archival as collected at time of first diagnosis or potentially at time of metastatic disease. This tissue may therefore potentially not reliably reflect the biomarker status at time of treatment start in the current study and subsequently influence the assessment of biomarker changes over time during study treatment.

Therefore, an optional biopsy collection has been included in this protocol to specifically evaluate these biomarker questions in the most accurate way. This optional biopsy collection program will require an additional consent from the patient and will enable the collection or use of biopsy material at baseline (just before Cycle 1, Day 1) and collection at Cycle 2, Day 1.

This additional consent will allow the collection of paired samples (pre-treatment and Cycle 2). PD-L1, CD8-positive T cells, and TILs in addition to other exploratory biomarkers will be evaluated on these samples.

3.3.5.3 Rationale for the Collection of Biopsy at the Time of Radiographic Progression

If deemed clinically feasible, patients will undergo a tumor biopsy collection at the first evidence of radiographic disease progression. Analysis of biological material (including, but not limited to, DNA and RNA) obtained from these specimens will help elucidate molecular changes associated with resistance, predictive of response to study drug, associated with progression to a more severe disease state, associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. RNA extraction will be done to enable gene expression analyses. DNA extraction on these samples will be done to enable analysis via e.g., whole genome sequencing (WGS) and/or next-generation sequencing (NGS) (e.g., whole exome or targeted sequencing).

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. If WGS data are generated, these will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

3.3.6 Rationale for Collection of PK and ATA Samples

Both atezolizumab and trastuzumab emtansine single-agent pharmacokinetics have been characterized in multiple Phase I, II, and III studies. Refer to the latest versions of the Trastuzumab Emtansine and Atezolizumab IBs for further details. In this study, PK/ATA samples will be collected from all patients in both Arm A and Arm B as detailed in [Appendix 2](#). Sparse sampling will be used in this study. PK and immunogenicity of atezolizumab (Arm B) and trastuzumab emtansine (Arm A and Arm B) will be assessed. The major objectives of the PK analysis for the current study are to characterize the pharmacokinetics of atezolizumab in the presence of trastuzumab emtansine and the pharmacokinetics of trastuzumab emtansine in the presence of atezolizumab. The trastuzumab emtansine results from Arm A and Arm B will be used to evaluate the trastuzumab emtansine pharmacokinetics in the presence and absence of atezolizumab in this BC patient population. The atezolizumab pharmacokinetics in the presence of trastuzumab emtansine will be evaluated and compared with historical data from single-agent atezolizumab studies.

3.3.7 Rationale for Allowing Patients to Continue Treatment Beyond Initial Progression per RECIST 1.1

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because radiographic PD does not necessarily reflect therapeutic failure (Section [3.3.5](#)). In the Phase Ia Study PCD4989g, several patients who progressed per RECIST v1.1 continued on atezolizumab treatment and subsequently demonstrated durable anti-tumor activity. Of the 21 patients with TNBC in the study who were evaluable for response (Section [1.2.2](#)), 3 patients with IC2/3 TNBC showed evidence of target lesion shrinkage after an initial increase in tumor burden or following the appearance of new lesions. These patients likely experienced pseudo progression or delayed response ([Emens et al. 2015](#)). Additionally, in some responding patients with NSCLC in Study PCD4989g, the growth of known lesions or the appearance of new radiographic lesions were shown to contain immune cells and no viable cancer cells on biopsy ([Gettinger et al. 2013](#)).

Pseudo-progression was observed in 3 out of 24 efficacy-evaluable patients who received atezolizumab in combination with nab-paclitaxel in Study GP28328 ([Adams et al. 2015](#)). The most commonly observed pattern was the appearance of new lesions

(e.g., FDG-avid lymph nodes) in the context of decreased overall tumor burden at the first or second tumor assessment.

The rate of progression or delayed anti-tumor immunity in (i) patients with HER2-positive metastatic breast cancer and/or (ii) when atezolizumab is administered in combination with trastuzumab emtansine is not known. To account for the possibility of pseudo-progression or delayed anti-tumor immunity, upon the identification per RECIST v1.1 progression, patients in this study may optionally continue to receive blinded study treatment provided they meet the criteria listed in Section 3.3. To mitigate the risk of continuing treatment in the face of true therapeutic failure, radiographic criteria for treatment discontinuation at the next scheduled assessment are described in Section 3.1.

For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; cystic changes or necrosis in existing lesions), the study permits treatment to 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 is suspected ([Appendix 4](#); [Eisenhauer et al. 2009](#)).

Although the primary efficacy endpoint of PFS will be analyzed based on investigator-assessed PFS using RECIST v1.1, a non-comparative analysis of the PFS, ORR, and DOR endpoint will be performed with use of immune-modified RECIST ([Appendix 5](#)) for eligible patients who continue treatment beyond radiographic progression, as an explorative endpoint of this study. The immune-modified RECIST instrument allows the incorporation of new lesions into the calculation of total tumor burden after baseline. As with the immune-related response criteria ([Wolchok et al. 2009](#)) it is recommended that radiographic progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudo progression/tumor immune infiltration.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll 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 within 6 months after completing adjuvant therapy. Patients must comply with the following inclusion and exclusion criteria.

4.1.1 Inclusion Criteria

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

- Age \geq 18 years.
- Signed written informed consent approved by the institution's Independent Ethical Committee/Institutional Review Board (IRB).

- Archival tumor samples must be obtained from primary and/or metastatic sites. Representative FFPE tumor specimens in paraffin blocks for central testing is required. Different material as described in [Appendix 3](#) may be accepted in exceptional cases (see Section [4.5.8.2.1](#)). Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated for HER2 and PD-L1 expression prior to enrollment.
- Patients must submit tumor tissue that is evaluable for PD-L1 expression to be eligible for this study. If multiple tumor specimens are submitted (e.g., an archival specimen [from initial BC diagnosis] and tissue from metastatic or LABC disease), patients may be eligible if at least one specimen is evaluable for PD-L1.

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

Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

- HER2-positive BC as defined by an IHC score of 3+ ([Appendix 6](#)) or gene amplified by in situ hybridization (ISH) as defined by a ratio of ≥ 2.0 ([Appendix 7](#)) for the number of HER2 gene copies to the number of chromosome 17 copies, prospectively tested by a Sponsor- designated central laboratory prior to enrollment. Both IHC and ISH assays will be performed; however, only one positive result is required for eligibility.

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

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

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

- Histologically or cytologically confirmed invasive BC: incurable, unresectable, locally advanced BC previously treated with multimodality therapy or MBC.
- Prior treatment for BC in the: adjuvant; unresectable locally advanced; or metastatic settings; which must include both, a taxane and trastuzumab (alone or in combination with another agent)
- Patients must have measurable disease that is evaluable per RECIST 1.1.

- ECOG Performance Status of 0 or 1.
- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):
 - Absolute neutrophil count ≥ 1500 cells/ μL (without granulocyte-colony stimulating factor [support] within 7 days prior to Cycle 1, Day 1)
 - Platelet count $\geq 100,000/\mu\text{L}$ (without transfusion within 7 days prior to Cycle 1, Day 1)
 - Hemoglobin ≥ 9.0 g/dL
 - Patients may be transfused or receive erythropoietic treatment to meet this criterion.
 - Albumin > 2.5 g/dL
 - AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ the upper limit of normal (ULN) with the following exceptions:
 - Patients with documented bone metastases: alkaline phosphatase $\leq 5 \times$ the ULN
 - Total bilirubin $\leq 1.5 \times$ the ULN
 - INR and aPTT $\leq 1.5 \times$ the ULN
 - This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
 - Calculated creatinine clearance ≥ 30 mL/min
- Negative serum pregnancy test within 7 days of enrollment for pre-menopausal women and for women less than 12 months after the onset of menopause.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of trastuzumab emtansine or 5 months after the last dose of atezolizumab/placebo, whichever is later.
 - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

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

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

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

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

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

The patient must have recovered from any resulting acute toxicity (to Grade \leq 1) prior to randomization.

- History of exposure to the following cumulative doses of anthracyclines as specified below.

Doxorubicin > 500 mg/m²

Liposomal doxorubicin > 500 mg/m²

Epirubicin > 720 mg/m²

Mitoxantrone > 120 mg/m²

Idarubicin > 90 mg/m²

If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m² doxorubicin.

- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence.
- Cardiopulmonary dysfunction as defined by:
 - Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg)
 - Inadequate left ventricular ejection function at baseline, <50% by either echocardiogram (ECHO) or multi-gated acquisition scan (MUGA)
 - History of symptomatic congestive heart failure (CHF)-Grade ≥ 3 per NCI CTCAE version 4.0 ([Appendix 8](#)) or Class \geq II New York Health Association
 - History of a decrease in left ventricular ejection function to <40% or symptomatic CHF with prior trastuzumab treatment
 - Myocardial infarction or unstable angina within 6 months of randomization
 - Current dyspnoea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
 - Serious cardiac arrhythmia not controlled by adequate medication
- Patients with severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures).
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment.
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis or active infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)
 - Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or HCV antibody. HIV, HBV, or HCV assessments are required at screening.
 - Patients who test positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV DNA.
 - Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.

- Need for current chronic corticosteroid therapy (≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)
 - Stable use (i.e., no change in dose within 3 months prior to Cycle 1, Day 1) of inhaled corticosteroids is allowed.
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for >2 weeks prior to randomization.
- Patients with known central nervous system (CNS) disease are not eligible, except for treated asymptomatic CNS metastases, provided that all of the following criteria are met:
 - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
 - No ongoing requirement for corticosteroids as therapy for CNS disease
 - No stereotactic radiation within 14 days prior to randomization
 - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
- Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Leptomeningeal disease
- Symptomatic pleural effusion, pericardial effusion, or ascites.
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.
 - Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.
 - Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade ≥ 3 peripheral neuropathy (according to the NCI CTCAE v4.0).
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins.
- History of autoimmune disease ([Appendix 10](#)), including, but not limited to, myasthenia gravis, autoimmune myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

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

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

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

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

Rash must cover < 10% of body surface area.

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

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

Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.

- Prior allogeneic stem cell or solid organ transplantation.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan.

Patients with a history of radiation pneumonitis in the radiation field (fibrosis) are eligible.

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

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

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

Stable use (i.e., no change in dose within 3 months prior to Cycle 1, Day 1) of inhaled corticosteroids is allowed

- Breastfeeding, or intending to become pregnant during the study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Number of Patients/Assignment to Treatment Groups

Approximately 200 patients will be enrolled in the study and randomized to treatment arms A and B in a 1:2 ratio (approximately 67 patients in Arm A and 133 patients in Arm B). An Interactive voice/ Web response system (IxRS) will be utilized to collect patient screening information and to randomize eligible patients to either treatment Arm A or B. Patients will be randomized within 28 days from initiation of screening. Patients will be blinded as to whether they receive atezolizumab or placebo in combination with trastuzumab emtansine. Investigators and study team members will also be blinded.

A permuted block randomization scheme will be used to achieve balance in treatment assignment within the two treatment arms with respect to pre-specified stratification factors (Section 4.2.2).

Patients who are randomized into this study will not be allowed to be re-randomized to receive a second course of study treatment.

Once a patient has been randomized into the study, the IxRS will be used to assign the kit numbers for study drugs to be dispensed at each treatment visit. It is important that the study drugs dispensed for each visit are the correct kit number, as assigned by the IxRS. This will ensure that drug use by dates and automatic study drug resupply to sites are managed appropriately via the IxRS.

4.2.2 Stratification

Randomization will be stratified based on the following *three* factors:

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

4.2.3 Study Treatment Unblinding

Unblinding of treatment assignment may occur either at patient or study level.

4.2.3.1 Unblinding at Patient Level

Unblinding of treatment assignment may occur either at patient or study level under the following two scenarios. The reason and date of unblinding should be documented in the electronic data capture (EDC) system.

4.2.3.1.1 Emergency Unblinding

Study treatment assignment may be unblinded for serious, unexpected study drug-related toxicity. Emergency unblinding should be a last resort performed only in cases where knowledge of treatment assignment will affect ongoing treatment of the patient. Investigators are permitted to perform emergency unblinding without prior approval from the Sponsor. However, they are encouraged to consult with the Medical Monitor prior to performing emergency unblinding.

4.2.3.1.2 Non-Safety Unblinding

Study treatment assignment for non-safety reasons may be unblinded only in situations where the patient is assessed as eligible for a clinical trial following discontinuation from the WO30085 study drug treatment and where the eligibility criteria requires the knowledge of prior treatment with cancer immunotherapy. This unblinding will require Sponsor assessment and approval.

4.2.3.2 Unblinding at Study Level

For regulatory reporting purposes, if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

Personnel responsible for performing PK and ATA assays will be unblinded to patients' treatment assignments to identify appropriate PK and ATA samples to be analyzed and assist with cleaning of PK and ATA data. While PK and ATA samples must be collected from patients assigned to the control arm to maintain the blinding of treatment assignment, PK and ATA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Samples from patients assigned to the control arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

4.3 STUDY TREATMENT

The investigational medicinal products (IMP) for this study are trastuzumab emtansine, atezolizumab, and placebo. Each will be labeled according to regulatory requirements in each country, as well as in accordance with International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and will be labeled for investigational use only. The Sponsor will provide trastuzumab emtansine, atezolizumab, and placebo free of charge to all study sites.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Trastuzumab Emtansine

The formulation, packaging, and handling should be performed according to the most recent version of the Trastuzumab Emtansine IB. For further details, refer to the Study Pharmacy Binder®.

4.3.1.2 Atezolizumab

The formulation, packaging and handling should be performed according to the most recent version of the Atezolizumab IB. For further details, refer to the Pharmacy Manual.

4.3.1.3 Placebo

The formulation of placebo is equivalent to atezolizumab but without the active agent. The handling of placebo should be followed as per Section [4.3.2.2](#).

4.3.2 Dosage, Administration, and Compliance

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 and dose must be re-adjusted for weight changes $\geq 10\%$ compared to the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed, following the dose reduction levels provided in [Table 4](#). 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.

Refer to [Table 1](#) for guidelines on administration of first and subsequent infusions of trastuzumab emtansine.

Table 1 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> • No premedication is administered. • Record patient's vital signs as indicated in Appendix 1 • Administer the initial dose as a 90 minute 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. 	<ul style="list-style-type: none"> • Record patient's vital signs as indicated in Appendix 1 • If prior infusions were well tolerated, subsequent doses may be administered as 30 minute infusions • Patient should be observed during the infusions and for at least 30 minutes after infusion.

4.3.2.2 Atezolizumab/Placebo

Patients will receive 1200 mg of atezolizumab/placebo administered by IV infusion q3w. Atezolizumab/placebo infusions will be administered according to the instructions outlined in [Table 2](#). Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section [5.1.3](#).

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.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Refer to [Table 2](#) for guidelines on administration of first and subsequent infusions of atezolizumab.

Table 2 Administration of First and Subsequent Infusions of Atezolizumab/Placebo

First Infusion	Subsequent Infusions
<ul style="list-style-type: none"> • No premedication is administered. • Record patient’s vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse (one vial in 250 mL NaCl) over 60 (± 15) minutes. • Record patient’s vital signs (heart rate • respiratory rate, blood pressure, and • temperature) during and after the infusion if clinically indicated • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. 	<ul style="list-style-type: none"> • If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician. • Record patient’s vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be administered over 30 (± 10) minutes. Continue to record vital signs within 60 minutes before starting infusion and during and after the infusion if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be delivered over 60 (± 15) minutes. • Record patient’s vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion 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 adverse events are provided in Section 5.1.

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

4.3.4 Investigational Medicinal Product Accountability

All IMPs for the study drugs used in this study (trastuzumab emtansine, atezolizumab, and placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs via the IxRS} to confirm the shipment arrival, condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site’s institutional standard operating procedure or returned to the Sponsor accompanied with the

appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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 Inventory Log.

4.3.5 Post-Trial Access to Trastuzumab Emtansine and Atezolizumab

The Sponsor will evaluate the appropriateness of continuing to provide trastuzumab emtansine and atezolizumab (where applicable) to patients on protocol treatment at the end of the study (*see Section 3.2 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:*

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study treatment to the study treatment discontinuation visit. All such medications must 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

The following therapies are permitted as concomitant medications in the study:

- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy is permitted to treat pre-existing bone metastases only
- Inactive influenza vaccinations during influenza season
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for prevention of skeletal related events

In general, investigators should manage patient's care with supportive therapies as clinically indicated and per local standards. No protocol specified pre-medication with steroids for the first infusion trastuzumab emtansine or atezolizumab/placebo is required. If pre-medication with steroids is being considered, please contact the Medical Monitor for approval.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2-receptor antagonist per standard practice (for sites outside the United States, equivalent medications may be substituted per local 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).

4.4.2 Prohibited Therapy

The following medications are prohibited while a patient is receiving study treatment:

- Traditional herbal medicines: These therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity.
- Concomitant use of potent cytochrome (CYP) P450 3A4/5 inhibitors (such as ketoconazole and itraconazole) with trastuzumab emtansine should be avoided. Consider an alternate medication with no or minimal potential to inhibit CYP3A4/5. If a strong CYP3A4/5 inhibitor needs to be co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions.
- Excessive alcohol intake should be avoided (occasional to moderate use is permitted).
- RANKL inhibitor (denosumab): Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study.
- Immunomodulatory agents, including, but not limited to, interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.
- Immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.

- 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.
- Any live, attenuated vaccine (e.g., FluMist[®]) at any time during the study

Systemic corticosteroids and anti-TNF- α agents may also attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, patients should not receive other immunomodulatory agents for 10 weeks after atezolizumab/placebo discontinuation.

4.5 STUDY ASSESSMENTS

Please see [Appendix 1](#) for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Signed, written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization into the study. The investigators will maintain a screening log to record details of all patients screened and to confirm eligibility or document reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

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

BC history includes prior cancer therapies and procedures.

Demographics will include age, gender, and self-reported race/ethnicity. Local HER2 testing information will also be collected.

4.5.3 Physical Examinations

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

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. 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.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Refer to [Appendix 1](#) for further details.

4.5.5 Tumor and Response Evaluations

All sites of measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in [Appendix 1](#); a time window of ± 7 days is allowed for all timepoints regardless of drug delays or interruptions. Tumor assessments will continue until disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Initial screening assessments must include CT scans (with oral or IV contrast unless contraindicated) or MRI scans of the chest, abdomen, and pelvis. A bone scan or positron emission tomography (PET) scan should also be performed to evaluate for bone metastases. MRI scans of the chest, abdomen, and pelvis or non-contrast CT scan may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. A MRI scan of the brain is required to confirm or refute a diagnosis of CNS metastasis at screening in the event of an equivocal scan. Patients with active or untreated CNS metastasis are not eligible for this study (Section [4.1.2](#) for CNS-related exclusion criteria).

If a CT scan for tumor assessment is performed as part of a PET/CT, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

CT scans of the neck should also be performed if clinically indicated during the screening period. At the investigator's discretion, other methods of assessment of measurable disease according to RECIST v1.1 may be used.

Evaluation of tumor response conforming to RECIST v1.1 ([Appendix 4](#)) and immune-modified RECIST ([Appendix 5](#)) will be performed every 6 weeks (± 7 days) following randomization, with additional scans performed as clinically indicated. The same radiographic procedures used to assess measurable disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT and/or MRI scans).

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of the following assessments every 6 weeks: 1) CT and/or MRI of the chest/abdomen/pelvis, as well as other known sites of disease, *including brain*, 2) If a patient has only bone as a site of involvement at screening which is determined to be measurable disease as per RECIST 1.1, then a bone scan or PET scan is mandated at every tumor assessment, otherwise, a bone scan or PET scan is to be performed as clinically indicated, e.g., suspicion of disease progression, 3) in cases where patients demonstrate control of their systemic disease but who newly develop isolated brain metastases and are eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments, *and* 4) any other imaging studies felt to be clinically indicated by the treating physician.

Response will be assessed by the investigator using RECIST v1.1 ([Appendix 4](#)) and immune-modified RECIST ([Appendix 4](#)) at each tumor assessment. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if PD is suspected. If the initial screening bone scan or PET scan indicates bone metastases and this is the only site of involvement and is determined to be measurable disease per RECIST 1.1, then a bone scan or PET scan needs to be performed every 6 weeks. If the screening scan shows evidence of either non-measurable bone metastases or no bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion. *If the brain is not identified as a site of involvement at screening, then brain CT or MRI only needs to be repeated beyond screening, if clinically indicated.* In cases where a patient demonstrates control of their systemic disease but who newly develops isolated brain metastases and is eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments (Section [3.1](#)).

If study drug treatment is discontinued prior to disease progression according to RECIST v1.1, tumor response assessment should continue to be performed as per the schedule specified in [Appendix 1](#).

In patients who continue treatment beyond radiographic disease progression per RECIST v1.1, tumor response will also continue to be assessed using immune-modified RECIST criteria as specified in [Appendix 1](#), until study treatment discontinuation.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints, if needed.

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 if LVEF declines are clinically suspected at the discretion of the investigator.

4.5.7 Electrocardiogram

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. 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 tracings. 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.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

4.5.8.1 Laboratory Samples

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

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin)
- Coagulation (aPTT and INR)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed every third cycle during treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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)
- Thyroid function test (thyroid-stimulating hormone [TSH], free T3, and free T4)
- HIV (tested prior to patient enrollment in the study)

HIV-positive patients are excluded from study participation.

- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], and anti-HBc)
 HBV DNA testing is required prior to or on Day 1 of Cycle 1 if a patient has negative serology for HBsAg and positive serology for anti-HBc.
 HCV serology (anti-HCV)

The assessments listed below will be performed at a central laboratory or by the Sponsor. Any remaining material from samples collected to enable these central assessments may be used for additional related safety assessments (e.g., ATA assay), exploratory biomarker profiling, and pharmacodynamic assay development purposes. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Central HER2 testing (for eligibility assessment) and PD-L1 testing (for stratification)
- Tumor and blood samples for RNA and DNA extraction for gene expression and genomic sequencing. If gene expression or genomic sequencing is performed, samples will be sent to one or more laboratories for analysis.
- Biomarker blood assays
 Blood samples will be processed to obtain blood cells, plasma, and serum for the determination of baseline level changes in surrogate pharmacodynamic biomarkers
- C-reactive protein
- Serum HER2 extra cellular domain at baseline
- ATA assays
 Serum samples will be assayed for the presence of ATAs to atezolizumab and trastuzumab emtansine using validated immunoassays.
- Auto-antibody testing: The baseline sample will be collected on Cycle 1, Day 1, prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected and will be analyzed centrally.
 Anti-nuclear antibody
 Anti-double-stranded DNA
 Circulating anti-neutrophil cytoplasmic antibody
 Perinuclear anti-neutrophil cytoplasmic antibody
- PK assays
 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.

4.5.8.2 Biomarker Samples

The schedule of tissue collection is described in [Appendix 3](#). Only at those sites where a legitimate site regulation renders submission of blocks impossible and only after having obtained the Sponsor's approval, submission of different material as described in [Appendix 3](#) may be accepted.

After completion of HER2 and PD-L1 testing, patient samples may also be tested with other exploratory assays/technologies to establish performance characteristics of these assays for both next generation diagnostic development and understanding treatment response associated to characteristics of the tumor microenvironment. Testing could be performed on all screened patients (screen-failed and enrolled) and will be performed only after eligibility is established for each patient. These exploratory testing data will have no impact on patient eligibility.

After initial HER2 and mandatory biomarker testing, the tissue blocks will be used for midterm storage up to the time of final clinical study report before returning them to sites to allow for future biomarker analysis. Hereafter, the blocks will be shipped back, unless the patient gives specific consent for the remainder of the samples to be stored for optional exploratory research (Research Biosample Repository [RBR]; Section 4.5.8). In cases where only slides were sent because of country or site regulations, a new request of slides will be sent to the sites in case additional markers or assays are defined up to final clinical study report. The midterm storage of tissue and the possibility of requesting more slides up to the time of the final clinical study report extends the possibility of deciding on analyses of important additional markers or assays while the study is ongoing or until final study data are available.

In cases where midterm storage of tumor tissue blocks is not allowed by local regulatory bodies (including IRB/EC policies) for patients without consent to RBR, the block will be sent back to the site no later than 3-6 months and requested at a later timepoint within the study in case additional analyses are defined. If the patient provides consent for optional exploratory research (RBR), the samples will be stored until no longer required in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

If tissue material from more than one timepoint was submitted, the midterm storage only applies to the most recent sample and the archival tumor tissue block for all patients enrolled will be returned no later than 3-6 months after eligibility determination. In case archival partial blocks or slides are sent, this tissue will not be returned.

All tissue blocks from patients who are not eligible to enroll in the study will be returned no later than 3-6 months after eligibility determination. [Figure 2](#) gives an overview of the tissue flow in the trial.

All biomarker samples taken during the study are summarized in [Table 3](#). Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in [Table 3](#). Such biomarker research may be required as science is rapidly and constantly evolving. Therefore, a definitive list of analyzed biomarkers may include other or additional parameters as well as novel or alternative technologies.

Table 3 Proposed Biomarkers for Exploratory Research

Sample Type	Timing	Biomarker
Breast Cancer Tumor tissue (See Appendix 3)	Mandatory Baseline (archival and/or metastatic) Optional Baseline (freshly taken) Cycle 2 (optional) Time of progression (mandatory, if clinically feasible)	<ul style="list-style-type: none"> • HER2 • PD-L1 • CD8 • Tumor Infiltrating Lymphocytes
DNA/RNA extracted from breast cancer tissue	Baseline, Cycle 2 and time of progression (if biopsy clinically feasible)	<ul style="list-style-type: none"> • Immune and cancer associated gene signatures (RNA) • Cancer related genes (DNA)
Plasma	Baseline and subsequent timepoints during treatment	<ul style="list-style-type: none"> • HER ligands
Serum	Baseline and subsequent timepoints during treatment	<ul style="list-style-type: none"> • Cytokines (e.g., IL-2, IFNg, IL-18)
DNA extracted from Whole Blood	Baseline (or later if missed at baseline)	Polymorphisms in: <ul style="list-style-type: none"> • PD-L1, PD-1 IL-8, IL-6, and related cytokines • Immune genes (NGS) Cancer related genes (NGS)
Circulating tumor DNA isolated from plasma	Baseline and subsequent timepoints during treatment	<ul style="list-style-type: none"> • ctDNA HER2 • ctDNA PIK3CA
(RNA extracted from) Peripheral blood mononuclear cells (PBMCs) isolated from whole blood ^a	Baseline (all patients) and subsequent timepoints during and after treatment (subset)	<ul style="list-style-type: none"> • Immune gene expression profiles (e.g. PD-L1, PD-1)

HER2=human epidermal growth factor 2; IL=interleukin; NGS=next-generation sequencing; PD-1=programmed death-1; PD-L1=programmed death-ligand 1.

^a Serial sample collection will be collected on approximately the first 50 enrolled patients only.

4.5.8.2.1 Tumor Tissue Samples

The schedule of tissue collection is described in [Appendix 3](#). Only at those sites where a legitimate site regulation renders submission of blocks impossible and only after having obtained the Sponsor's approval, submission of different material as described in [Appendix 3](#) may be accepted.

After completion of HER2 and PD-L1 testing, patient samples may also be tested with other exploratory assays/technologies to establish performance characteristics of these assays for both next generation diagnostic development and understanding treatment response associated to characteristics of the tumor microenvironment. Testing could be performed on all screened patients (screen-failed and enrolled) and will be performed only after eligibility is established for each patient. These exploratory testing data will have no impact on patient eligibility.

After initial HER2 and mandatory biomarker testing, the tissue blocks will be used for midterm storage up to the time of final clinical study report before returning them to sites to allow for future biomarker analysis. Hereafter, the blocks will be shipped back, unless the patient gives specific consent for a remainder of the samples to be stored for optional exploratory research (RBR; Section [4.5.8](#)). In cases where only slides were sent because of country or site regulations, a new request of slides will be sent to the sites in case additional markers or assays are defined up to final clinical study report. The midterm storage of tissue and the possibility of requesting more slides up to the time of the final clinical study report extends the possibility of deciding on analyses of important additional markers or assays while the study is ongoing or until final study data are available.

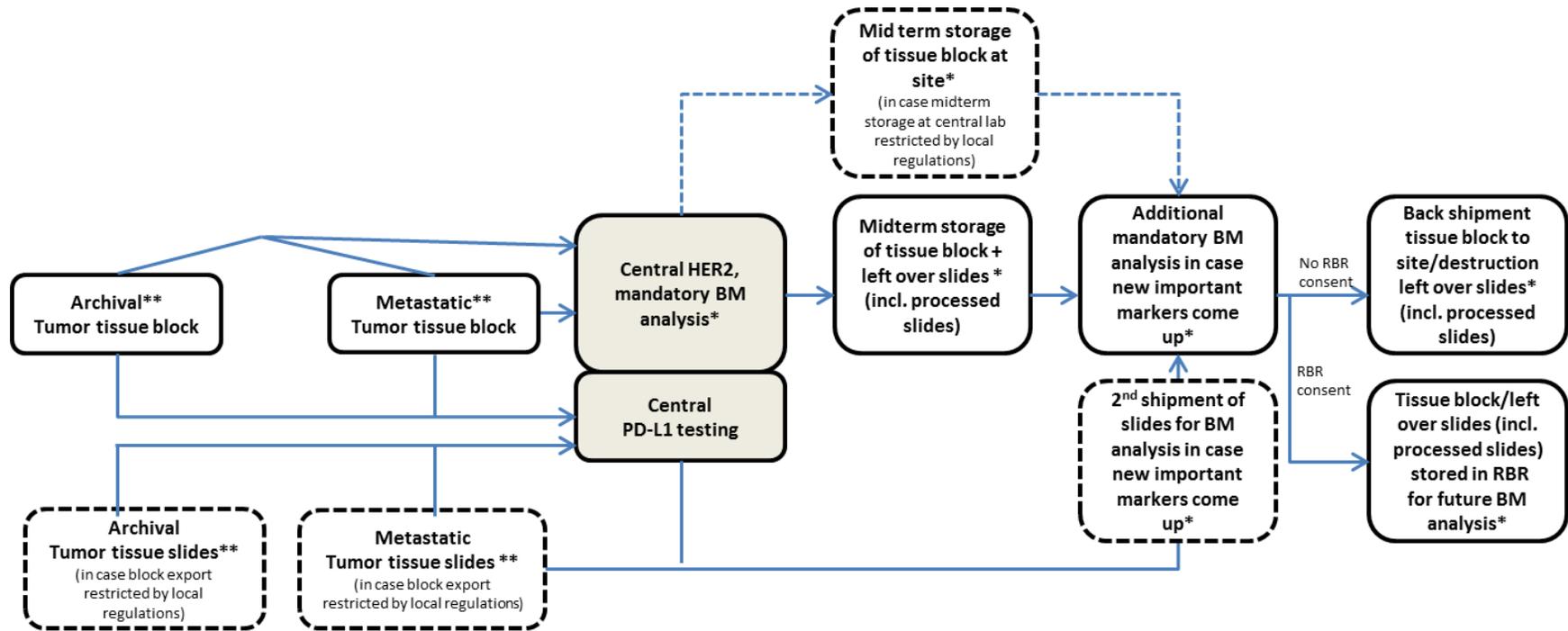
In cases where midterm storage of tumor tissue blocks is not allowed by local regulatory bodies (including IRB/EC policies) for patients without consent to RBR, the block will be sent back to the site no later than 3-6 months and requested at a later timepoint within the study in case additional analyses are defined. If the patient provides consent for optional exploratory research (RBR), the samples will be stored until no longer required in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

If tissue material from more than one timepoint was submitted, the midterm storage only applies to the most recent sample and the archival tumor tissue block for all patients enrolled will be returned no later than 3-6 months after eligibility determination. In case archival partial blocks or slides are sent, this tissue will not be returned.

All tissue blocks from patients who are not eligible to enroll in the study will be returned no later than 3-6 months after eligibility determination.

[Figure 2](#) gives an overview of the tissue flow in the trial.

Figure 2 Overview of Tissue Flow in the Study



BM = biomarker; CSR = clinical study report; RBR = research biosample repository.

* Central HER2 and PD-L1 testing is performed on all patients, but mandatory BM analysis and mid-term storage of tissue will only be performed on randomized patients; mid-term storage is until CSR finalization.

** If both archival and metastatic tissue is available, both will be tested for PD-L1, while for HER2 only one sample will be used.

DNA and RNA from collected tumor tissue will be extracted and may enable targeted sequencing or whole exome sequencing (NGS and gene expression based methods) for exploratory research (that may include, but is not limited to, immune or cancer-related genes, PIK3CA mutation, mutational load and biomarkers associated with common molecular pathways).

NGS may be conducted by Foundation Medicine on samples collected at time of disease progression. If performed by Foundation Medicine, the investigator can obtain results from the samples collected at the time of disease progression in the form of an individualized report per patient, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

4.5.8.2.2 Blood Samples

Blood samples are taken for cells, plasma, and serum collection ([Table 3](#)). Whole blood samples may be analyzed by fluorescence-activated cell sorting and processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., proteins, RNA and DNA). Serial whole blood samples for PBMC collection will be taken on approximately the first 50 patients only.

Blood samples collected during the study may be evaluated for immune-related, tumor type-related, and other exploratory biomarkers (e.g., genetic alterations determined by DNA sequencing methods which may include NGS, and/or alterations in gene expression ([Section 4.5.9](#))).

4.5.9 Biomarker Sample Handling and Biomarker Results

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

Given the complexity and exploratory nature of biomarker analyses, results from these analyses will not be shared with investigators or study participants, unless required by law, with the exception of NGS data on Disease Progression Samples in case performed by Foundation Medicine.

The remaining samples obtained for study-related procedures will be destroyed no later than 5 years post final clinical study report has been completed, unless patient has consented to RBR ([Section 4.5.10](#)).

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.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens 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.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- 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

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB or Ethics Committee (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](#)) will not be applicable at that site.

4.5.10.3 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 or disease under study:

- Residual from tumor tissue block or slides
- Whole Blood samples collected at baseline

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored

in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

RBR specimens 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).

4.5.10.4 Confidentiality

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

Patient medical information associated with RBR specimens 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.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law except if the analysis is performed by [REDACTED]. 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 specimens 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.

4.5.10.5 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 specimens 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 specimens. 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(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WO30085 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WO30085.

4.5.10.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with GCP 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 specimens 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 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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 withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time (and for any reason)
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues on the study
- Investigator or Sponsor determines it is in the best interest of the patient to discontinue from the study
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another systemic anti-cancer therapy
- Pregnancy
- Radiographic disease progression according to RECIST v1.1, with the following exception:

Patients may receive blinded atezolizumab/placebo in combination with trastuzumab emtansine until unacceptable toxicity or loss of clinical benefit, provided they meet all of the criteria specified in Section 3.1. Patients must provide written consent to acknowledge deferring any standard treatment options that may exist in favor of continuing study treatment at the time of initial progression.

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site 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 adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigators if the study is placed on hold or if the Sponsor has decided to discontinue the study or the development program.

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 ICH guideline for GCP
- No study activity (i.e., all patients have completed 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. Patients will undergo safety monitoring by an iDMC (Section 9.4) during the study, including assessment of the nature, frequency, and severity of adverse events; details of this safety monitoring will be specified in the iDMC Charter. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

Please refer to the latest versions of the trastuzumab emtansine and Atezolizumab IBs for a complete and most up to date summary of safety information.

5.1.1 Risks Associated with Trastuzumab Emtansine

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. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at risk of pulmonary events.

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

Guidelines for management of trastuzumab emtansine in patients who develop ILD or pneumonitis are provided in Section 5.1.4.2.

5.1.1.2 Hepatotoxicity

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

- Serious hepatobiliary 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 Section [5.1.4.3](#).

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](#) 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 Section [5.1.3.2.3](#).

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 trastuzumab emtansine 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 trastuzumab emtansine, as described in Section [4.3.2.1](#).

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in Section [5.1.4.1](#).

5.1.1.5 Hematologic Toxicity

Thrombocytopenia has been reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (platelet count $\geq 50,000/\mu\text{L}$), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (platelet count $\geq 75,000/\mu\text{L}$) by the next scheduled dose (i.e., within 3 weeks). In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

Patients with thrombocytopenia ($\leq 100,000/\text{mm}^3$) and patients on anti-coagulant treatment should be monitored closely during treatment with trastuzumab emtansine. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Trastuzumab emtansine has not been studied in patients with platelet counts $\leq 100,000/\text{mm}^3$ prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater ($< 50,000/\text{mm}^3$), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq 75,000/\text{mm}^3$).

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 Section 5.1.3.2.2.

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 Section 5.1.3.2.3.

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. 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

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such atezolizumab therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. To date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, myocarditis, hypophysitis, and meningoencephalitis. *In addition, systemic immune activation (described below) is a potential risk when atezolizumab is given in combination with other immunomodulating agents.* For further details regarding the up-to-date clinical safety of atezolizumab, see the most recent version of the Atezolizumab IB.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- *CBC with peripheral smear*
- *PT, PTT, fibrinogen, and D-dimer*
- *Ferritin*
- *Triglycerides*

- *AST, ALT, and total bilirubin*
- *LDH*
- *Complete neurologic and abdominal examination (assess for hepatosplenomegaly)*

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010).

Suggested workup and management guidelines for overlapping toxicities between atezolizumab and trastuzumab emtansine (i.e., IRR and Hypersensitivity reactions, suspected hepatotoxicity and pneumonitis) are provided in Section 5.1.4.

5.1.3 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.

5.1.3.1 Dose Modification

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 adverse events will be graded according to the NCI CTCAE v4.0.

- 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 accordingly.
- 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.
- Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

- 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 adverse events for >42 days beyond when the next dose would have been given, then the patient will be discontinued from atezolizumab or placebo treatment and will be followed for safety and efficacy as specified in Section 3.1. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab or placebo after a hold >42 days, study drug may be restarted with the approval of the Medical Monitor.

If patients must be tapered off steroids for the treatment of adverse events related to atezolizumab or placebo, study treatment may be withheld for >42 days until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

- 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 (in consultation with the Sponsor’s Medical Monitor or designee when appropriate). 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 4), at the discretion of the investigator. Subsequent cycles should remain q3w, and patients should be assessed for toxicity as described in Section 5.1.3. If a patient requires a dose reduction, dosing will be reduced by one dose level as per Table 4.

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 Adverse Event 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 4 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.

5.1.3.2 Management of Patients who have Trastuzumab Emtansine Related Specific Adverse Events

5.1.3.2.1 Cardiotoxicity

Patients without significant cardiac history and with a baseline LVEF of $\geq 50\%$ 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](#)).

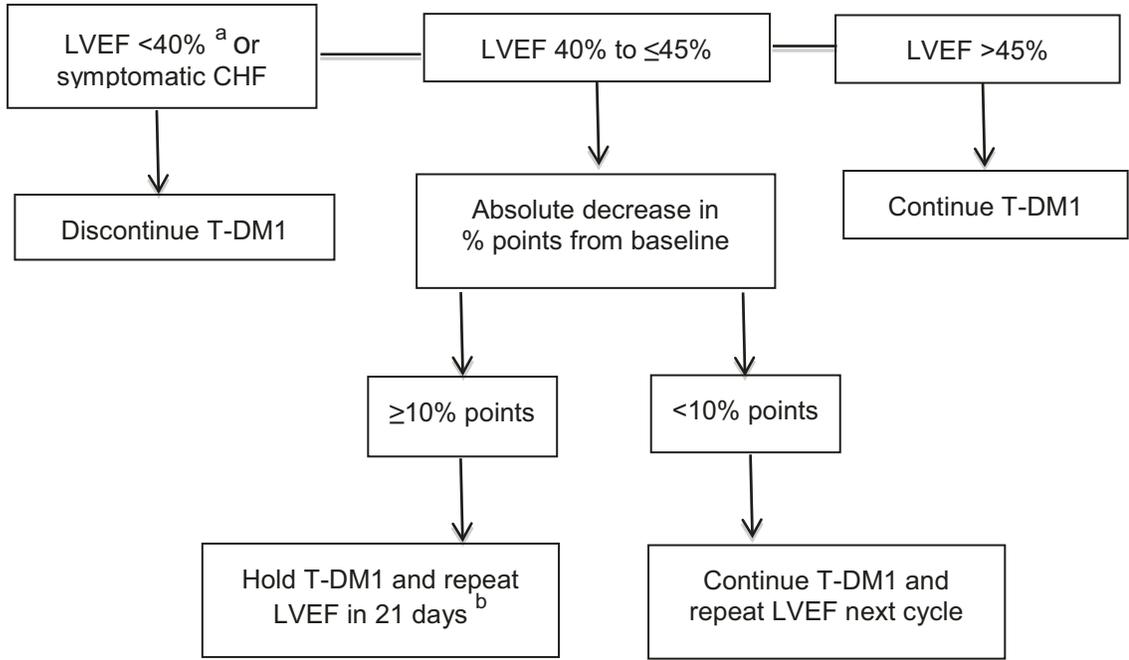
[Figure 3](#) summarizes the management of trastuzumab emtansine on the basis of LVEF measurements and changes in LVEF from baseline in patients. If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine 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 3](#) for *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 $\geq 10\%$ 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 3 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.

5.1.3.2.2 Hematological Toxicities

See [Table 5](#) for trastuzumab emtansine dose modification guidelines for hematological toxicities, including thrombocytopenia.

Table 5 Trastuzumab Emtansine Dose Modification Guidelines for Hematological Toxicity

Event	Action to Be Taken
Grade 2 thrombocytopenia (50,000 to 75,000/ μ L)	Assess platelet counts weekly or as medically indicated until recovery. Withhold study treatment until Grade \leq 1. Resume treatment without dose reduction.
Grade 3 thrombocytopenia (25,000 to < 50,000/ μ L)	Withhold trastuzumab emtansine until recovery to Grade \leq 1 (\geq 75,000/ μ L). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (< 25,000/ μ L) at any time	Withhold trastuzumab emtansine until recovery to Grade \leq 1 (\geq 75,000/ μ L). Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 1 within 42 days after the last dose received.
Grade \geq 3 hematologic toxicity other than thrombocytopenia	Withhold trastuzumab emtansine until recovery to Grade \leq 2. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 2 within 42 days after the last dose received.

5.1.3.2.3 Neuropathy

See [Table 6](#) for trastuzumab emtansine dose modification guidelines for neuropathy.

Table 6 Trastuzumab Emtansine Dose Modification Guidelines for Neuropathy

Event	Action to Be Taken
Grade \geq 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade \leq 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 \leq 2 within 42 days after the last dose received.

5.1.3.3 Management of Patients Who Have Atezolizumab/Placebo-Related Specific Adverse Events

For details on the management of infusion-related reactions and all other immune-related adverse events, including but not limited to, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic, or eye toxicity, refer to the most recent version of the Atezolizumab IB.

Guidelines for the management of patients who experience specific adverse events (other than systemic immune activation) are provided in the most recent version of the Atezolizumab IB.

No dose modification for atezolizumab is allowed.

5.1.4 Management of Patients who have Potential Overlapping Toxicities Associated with Trastuzumab Emtansine and Atezolizumab/Placebo

5.1.4.1 Infusion-Related Reactions

No premedication is indicated for the administration of atezolizumab/placebo in Cycle 1. Patients who experience an IRR at Cycle 1 of atezolizumab/placebo treatment may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Table 7 Management Guidelines for Atezolizumab/Placebo Infusion-Related Reactions

Severity	Management
Grade 1	<ul style="list-style-type: none">• Reduce infusion rate to half the rate being given at the time of event onset.• After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.• If tolerated, the infusion rate may then be increased to the original rate.
Grade 2	<ul style="list-style-type: none">• Interrupt atezolizumab/placebo infusion.• Administer aggressive symptomatic treatment.• Restart only after the symptoms have adequately resolved to baseline grade.• The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.• At next cycle, administer oral premedication with antihistamine and anti-pyretic and monitor closely for infusion reaction.
Grades 3–4	<ul style="list-style-type: none">• Stop infusion.• Proper medical management which may include oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen• Discontinue atezolizumab/placebo treatment.• Contact the Medical Monitor if atezolizumab/placebo is discontinued.

IRR = infusion-related reactions; IV = intravenous.

Table 8 Management Guidelines for Trastuzumab Emtansine Infusion-Related Reactions (Caused by Cytokine Release) or Hypersensitivity (Allergic) Reaction

Event	Action to Be Taken
Grade 2 reaction	<p>Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms.</p> <p>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 at the investigator's discretion.</p>
Grade 3 reaction	<p>Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms.</p> <p>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.</p> <p>Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.</p>
Grade 4 reaction	<p>Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms.</p> <p>Discontinue trastuzumab emtansine.</p>

5.1.4.2 Pulmonary Events: Atezolizumab and Trastuzumab Emtansine

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

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 9](#) for management guidelines for pulmonary events and pneumonitis.

In this study, atezolizumab and trastuzumab emtansine are discontinued for all grades of interstitial lung disease and pneumonitis. Refer to Section [5.1.4.2](#) for details on trastuzumab emtansine and pulmonary events.

Table 9 Management Guidelines for Interstitial Lung Disease and Pneumonitis

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
Grade 1 – 4	Discontinue atezolizumab/placebo treatment Refer to the most recent version of the Atezolizumab IB for further management guidance	Discontinue trastuzumab emtansine treatment.

IB = Investigator’s Brochure.

5.1.4.3 Hepatic Events: Atezolizumab and Trastuzumab Emtansine

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Liver function will be monitored throughout study treatment.

While on this study, patients who present 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 10](#) for management guidelines for atezolizumab/placebo and trastuzumab emtansine hepatic events.

Note: No dose modification for atezolizumab/placebo is indicated on the basis of hyperbilirubinemia alone.

Table 10 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
ALT or AST increase that meets Hy's law criteria: ALT or AST > 3 × ULN in combination with TBILI > 2 × ULN or clinical jaundice	Discontinue atezolizumab/placebo treatment.	Discontinue trastuzumab emtansine treatment.
ALT or AST increase that does not meet Hy's law criteria ALT/AST Grade 1 (> 1.0–3.0 × ULN)	Treat at the same dose level. Continue LFT monitoring.	Treat at the same dose level.
ALT/AST Grade 2 (> 3.0–5.0 × ULN)	Withhold atezolizumab/placebo dose. If persists > 5–7 days: Consider starting 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 ≤ 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.	Treat at the same dose level.

Table 10 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
ALT/AST Grade 3 ($> 5.0-20.0 \times \text{ULN}$)	<p>Discontinue atezolizumab/placebo dose.</p> <p>Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary.</p> <p>Start 60 mg prednisone or equivalent per day.</p> <p>If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered.</p> <p>Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1.</p> <p>Contact the Medical Monitor if atezolizumab/placebo treatment is discontinued.</p>	<p>Withhold trastuzumab emtansine dose.</p> <p>Do not administer trastuzumab emtansine until recovery to Grade ≤ 2, and then resume with dose reduction by one level.</p> <p>Discontinue trastuzumab emtansine treatment if the event has not resolved to Grade ≤ 2 within 42 days after the last dose received.</p>
ALT/AST Grade 4 ($> 20.0 \times \text{ULN}$)	<p>Discontinue atezolizumab/placebo treatment.</p> <p>Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary.</p> <p>Start 60 mg prednisone or equivalent per day.</p> <p>If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered.</p> <p>Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1.</p> <p>Contact the Medical Monitor if atezolizumab/placebo treatment is discontinued.</p>	<p>Discontinue trastuzumab emtansine treatment.</p> <p>Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.</p>

Table 10 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
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 atezolizumab/placebo treatment	Discontinue trastuzumab emtansine 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.

5.1.4.4 Hyperbilirubinemia: Trastuzumab Emtansine

See [Table 11](#) for dose modifications of trastuzumab emtansine for hyperbilirubinemia.

Table 11 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 until total bilirubin recovers to Grade ≤ 1 and then resume at the same dose level.
Grade 3 (> 3 to $\leq 10 \times$ ULN)	Withhold 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.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, 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 GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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), except as described in Section [5.3.5.10](#)
- 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, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- 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)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
 - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (Section [5.3.5.11](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event 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 drug
- 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 adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; Section [5.3.3](#)); the event itself may be of relatively minor medical significance and thus deemed "not serious" (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after becoming aware 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 are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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 (Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, 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 the study drug is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, or hyperthyroidism
- Hepatitis
- Transaminitis Grade ≥ 2 (AST or ALT $> 3 \times$ the ULN and bilirubin $> 2 \times$ the ULN or AST/ALT $> 10 \times$ the ULN)
- Systemic lupus erythematosus
- Neurological: Guillain-Barré syndrome, myasthenia gravis, and meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation (SIA), and infusion-reaction syndrome

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (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 and 5.6.

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

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, 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 drug**, only serious adverse events 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 serious adverse events).

After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study drug or initiation of another anti-cancer therapy (whichever occurs first).

Serious adverse events and adverse events of special interest will continue to be reported (independent of causality) until 90 days after the last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that occur after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug), if the event is believed to be related to prior treatment with study drug, regardless if the patient has initiated another anti-cancer therapy treatment (Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event 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 adverse event severity grading scale as per the latest NCI CTCAE (v4.0) will be used for assessing adverse event severity. [Table 12](#) will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE v4.0.

Table 12 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE v4.0

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 (v4.0), 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 adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug 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 13 Causal Attribution Guidance

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

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 and avoid colloquialisms and abbreviations when recording adverse events on the Adverse Event eCRF.

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction or allergic reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related [or] allergic reactions (Section 5.3.5.1), 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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event 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, adverse events 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 adverse event 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 a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events 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 adverse event 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 adverse event 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 serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event 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 adverse event. A laboratory test result must be reported as an adverse event 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 adverse events.

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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ 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 adverse event. 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event 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 adverse event.

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ 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 (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 a serious adverse event or an adverse event of special interest (Section 5.4.2).

Nodular Regenerative Hyperplasia

NRH, whether or not accompanied by abnormal LFTs, should be reported to the Sponsor as a serious adverse event.

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (Section 5.3.1) that are attributed by the investigator solely to progression of MBC should be recorded on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (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").*

During survival follow-up, deaths attributed to progression of MBC should be recorded on the Survival eCRF.

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 adverse event 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 Metastatic Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. 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 adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event 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 adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- 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 adverse event
- Hospitalization due solely to progression of the underlying MBC

An event that leads to hospitalization under the following circumstances is not considered to be serious adverse event, but should be reported as adverse events 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 adverse event, but does not meet the definition of an overnight admission (e.g., tooth extraction)

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, unless it results in untoward medical.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 5.4.2).

Adverse events associated with an overdose of trastuzumab emtansine in previous clinical studies include thrombocytopenia and increased ALT. There was one case of overdose in which the patient died. No information on overdose has been established at this time for atezolizumab.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting from the investigator to the Sponsor to allow the Sponsor to immediately put into place appropriate measures to address potential new risks in this or related clinical trials. 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 drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.2.3 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events 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 serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor [REDACTED] M.D.
Telephone No.: [REDACTED]
Mobile Telephone No.: [REDACTED]

Medical Monitor [REDACTED] Ph.D.
Telephone No.: [REDACTED]
Mobile Telephone No.: [REDACTED]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all 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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting 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 Drug Initiation

After initiation of study drug, all serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug (regardless of causality) or until initiation of new systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study treatment until initiation of new systemic anti-cancer therapy after the last dose of study treatment, 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, generate a report and submit the report via the EDC system to Roche Safety Risk Management.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting 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 post-study adverse events 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 to immediately inform the investigator if they become pregnant during the treatment period and for 5 months after the last dose of atezolizumab/placebo or 7 months after the last dose of trastuzumab emtansine, whichever occurs last.

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 serious adverse events 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. Additional information on any atezolizumab/placebo or trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). 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.

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 trastuzumab emtansine.

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. 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 drug. When permitted by the site, the pregnant partner would need to sign an Authorization for 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 when updated information on the course and outcome of the pregnancy becomes available. Additional information on any atezolizumab/placebo or trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). 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

Any abortion should be classified as a serious adverse event (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; Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the study period, resolution of adverse events (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.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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. Pathologic material, if already obtained to evaluate the event, may be requested for review.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After initiation of study treatment, all adverse events will be reported 30 days after the last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Serious adverse events and adverse events of special interest will continue to be reported (independent of causality) until 90 days after the last dose of study drug or until initiation of new systemic anti-cancer therapy, whichever occurs first.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that occur after 90 days after the last dose of study drug (Section 5.3.1), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

During survival follow-up, deaths attributed to progression of MBC should be recorded on the Death Attributed to Progressive Disease eCRF.

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

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest 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 adverse event cases, the Sponsor will assess the expectedness of these events using the most recent version of the following reference documents:

- Trastuzumab Emtansine IB
- Atezolizumab IB

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.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will regularly monitor the incidence of the above-listed anticipated events during course of 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 primary efficacy endpoint for this study is PFS based on investigator tumor assessment. *The primary PFS analysis will be performed when approximately 115 PFS events have occurred.*

With approximately 200 patients randomized according to a 1:2 randomization (approximately 67 patients will be randomized to Arm A and approximately 133 patients will be randomized to Arm B) the study has the estimated power for the PFS HRs presented in [Table 14](#).

Table 14 Estimated Power at *Primary* PFS Analysis for Different PFS HRs

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

HR=Hazard ratio; PFS=progressive-free survival.

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

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

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

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, BC 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 BC diagnosis. Frequency counts will be presented by treatment arm for categorical variables such as gender, race, and age category.

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

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

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

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

The Kaplan-Meier method will be used to estimate median PFS and the corresponding 95% CIs for each treatment arm. The 2-sided log-rank test, stratified by the factors specified in Section 4.2.2 (excluding liver metastases), will be used to compare PFS between the treatment arms at the overall two-sided significance level of 5%. Liver metastases will be excluded because of the potential that some of the strata may have very few patients, which would result in a loss of power. The stratification factors will be based on data collected by the IxRS rather than on data collected on the eCRFs. The unstratified log-rank test result will also be provided. The Cox proportional hazards model, stratified by the previous noted stratification factors, excluding liver metastases, will be used to estimate the HR and to calculate the 95% CI of the HR.

The *primary* PFS analysis will be performed when approximately 115 investigator-assessed PFS events have been observed and is anticipated to occur approximately 15 to 17 months from FPI, depending on PFS HR assumptions (Section 6.1).

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

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

Further methodological details will be provided in the SAP.

6.4.2 Secondary Efficacy Endpoints

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

Overall Survival

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

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

Objective Response Rate

Objective response, defined as a CR or PR, will be determined by investigator tumor assessment using RECIST 1.1. *Only patients with measurable disease at baseline will be included in the analysis of objective response.* Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified according to the factors specified in Section 4.2.2 (*excluding liver metastases*) will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

Duration of Response

DOR is defined as the time from first occurrence of a documented objective response (PR or CR) to disease progression, as determined by investigator tumor assessment

using RECIST 1.1, or death from any cause, whichever occurs first. The analysis methods are similar to those described for the primary efficacy endpoint PFS. The limitations of this responder analysis are acknowledged.

6.4.3 Exploratory Efficacy Endpoints

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

PFS Assessed in the PD-L1 Selected Subgroup

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

PFS Assessed using Immune-Modified RECIST

PFS is defined as the time from randomization to first occurrence of disease progression as determined by investigator assessment using immune-modified RECIST or death from any cause, whichever occurs earlier. Only patients who are clinically eligible for treatment beyond disease progression (as defined in Section 3.1) will be included in this analysis. The analysis methods are similar to those described for the primary efficacy endpoint.

Objective Response Rate based on Immune Modified RECIST

Objective response, defined as a complete response (CR) or partial response (PR), will be determined by investigator tumor assessment using immune-modified RECIST. Patients without a post-baseline tumor assessment will be considered non-responders. Objective responses must be confirmed at least 28 days after the initial documentation of response. An estimate of the ORR and its 95% CI (Blyth-Still-Casella) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel Chi-squared test stratified according to the factors specified in Section 4.2.2 (*excluding liver metastases*) will be used to compare response rates between treatment arms. An unstratified Chi-squared test will also be provided. Finally, the difference in response rates between treatment arms will be computed with 95% CIs, using the normal approximation to the binomial distribution.

Duration of Response *based on Immune-Modified RECIST*

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

1-Year Survival Rate

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

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.

Study Drug Exposure

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

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

Adverse Events

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

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

- All adverse events
- Serious adverse events
- Adverse events leading to death
- Adverse events leading to study drug discontinuation
- Adverse events leading to dose reduction
- *Sponsor-defined adverse events of special interest*

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

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

Additional *safety* analyses may be performed as indicated.

Laboratory Data

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

6.6 PHARMACOKINETIC ANALYSES

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

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

Additional PK and PD analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

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

Methodological details on immunogenicity analyses will be described in the SAP.

6.8 BIOMARKER ANALYSES

Descriptive statistics will be utilized for the analysis and reporting of the exploratory biomarker objectives outlined in Section 4.5.8.2. This may include appropriate multivariate analyses. Further details can be found in the SAP.

6.9 INTERIM ANALYSIS

There is no planned interim efficacy analysis for PFS.

Overall safety will be monitored on a regular basis by an iDMC. Further details, including iDMC composition and meeting frequency, will be provided in the iDMC Charter.

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 any 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.

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 7.5.

To facilitate source data verification, 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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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 (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) 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.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. 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 (Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events 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

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.

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.

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 (i.e., 1 year after last patient last visit [LPLV]).

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 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.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd.

Treatment assignment will be handled through the IxRS system. 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.

Tumor assessment scans will be collected prospectively by the Sponsor in the event that an independent review facility (IRF) will be utilized.

A Steering Committee (SC) will be set up to provide guidance on the protocol, study design and the statistical analysis plan, 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 patient safety data in unblinded fashion 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.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of this trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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 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.

9.6 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

- 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).
- 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.
- 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.
- 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.
- Bianchini G, Pusztai L, Pienkowski T et al. Immune modulation of pathologic complete response after neoadjuvant HER2-directed therapies in the NeoSphere trial. *Ann Oncol*. 2015;26:2429–36.
- 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.
- 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.
- 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.
- Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol*. 2014;25:1871–88.
- Chen G, Gupta 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.
- Diéras V, Miles D, Verma S, et al. Trastuzumab Emtansine (T-DM1) Improves Overall Survival Versus Capecitabine Plus Lapatinib in Patients With Previously Treated HER2-Positive Advanced Breast Cancer: Final Results From the Phase 3 EMILIA Study. San Antonio Breast Cancer Symposium, December 8-12, 2015.

- Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol* 2010;37:499–507.
- 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, Braithen 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.
- Food and Drug Administration. Drugs at FDA [resource on the Internet]. 2016 [cited 2016 November 28]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/.
- 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.
- Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-1 antibody MPDL3280 in cancer patients. *Nature* 2014;515:563–7.
- International Agency for Research on Cancer. Globocan 2012; [resource on the internet]. Available from: <http://www-dep.iarc.fr>.
- Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annual Rev Immunol* 2008;26:677–704.
- Krop I, Kim S-B, 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 Oncology*. 2014;15:689–699.
- 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.
- Müller P, Kreuzaler P, Khan T, et al. Trastuzumab emtansine (T-DM1) renders HER2+ breast cancer highly susceptible to CTLA-4/PD-1 blockade. *Sci Transl Med*. 2015;7:315.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: invasive breast cancer, version 3.2014. Available at http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. 2014a.
- 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.

- 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.
- 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 Mar 4.
- Rubin I, Yarden Y. The basic biology of HER2. *Ann Oncol* 2001;12(Suppl 1):S-8.
- 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. Clinical activity and safety from a phase II study (FIR) of MPDL3280A (anti-PDL1) in PD-L1 selected patients with non-small cell lung cancer (NSCLC). Proceedings of the 51st ASCO Annual Meeting:2015 Jun 3-7: Chicago. Available from: <http://meetinglibrary.asco.org/content/108536?media=vm>.
- Spira A, Park K, Mazieres J et al. Efficacy, safety and predictive biomarker results from a randomized phase II study comparing MPDL3280A vs docetaxel in patients with advanced NSCLC (POPLAR). Proceedings of the 51st ASCO Annual Meeting:2015 Jun 3-7: Chicago. Available from: <http://meetinglibrary.asco.org/content/150315-156>.
- 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.
- Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Eng J Med* 2012;367:1783–91.
- Wildiers H, Sung-Bae K, Antonio Gonzalez M et al. Trastuzumab emtansine (T-DM1) improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: final overall survival results from the phase 3 TH3RESA study. San Antonio Breast Cancer Symposium, December 8–12, 2015.
- 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.

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 Assessments

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

Appendix 1 Schedule of Assessments (cont.)

Assessment or Procedure	Screening Period	Treatment Period (Cycles 1 through Study Treatment Discontinuation)	Study Treatment Completion/Early Discontinuation ^a	Follow-Up (± 14 Days) ^b
	Days –28 to –1	Day 1 (± 3 Days)		
Bone scan/PET ^q	x	Perform as clinically indicated or as scheduled tumor assessment if only bone involvement at baseline		
CT or MRI of Brain ^r	Mandatory at screening	Perform as clinically indicated or as scheduled tumor assessment ^r		
12-Lead electrocardiogram ^s	x	Perform as clinically indicated		
NYHA classification	x			
ECHO or MUGA scan ^t	x	x Day 15–21 of Cycle 1, every fourth cycle thereafter. Additional LVEF measurements may be performed if LVEF declines are clinically suspected at the discretion of the investigator	x If not performed within 6 weeks of this visit	
Atezolizumab/placebo administration		x ^w		
Trastuzumab emtansine administration		x ^x		
PK/ATA		x (See Appendix 2)	x	
Blood Sample for Biomarker Analysis		x (See Appendix 3)	x	
Sample for auto-antibodies ^u	x			
Tissue Sample for Biomarker Analysis ^v		x (See Appendix 3)	x	
Concomitant medications	x	x	x	

Appendix 1 Schedule of Assessments (cont.)

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

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

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

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

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

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

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

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

Appendix 1 Schedule of Assessments (cont.)

- ^e Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the Cycle 1, Day 1 visit. Breast cancer history includes prior cancer therapies and procedures.
- ^f Refer to [Appendix 3](#) for tissue requirements related to eligibility. HER2 and or PDL-1 status may be determined outside of the screening window of 28 days.
- ^g A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^h A limited physical examination consists of a symptom-driven physical examination that focuses on organ systems related to potential and ongoing adverse events and is based on the patient's clinical course during study treatment, the patient's medical history, and/or the known adverse event profiles of the study medications. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ⁱ Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline.
- ^j Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital signs should be obtained and reviewed before and after each study treatment administration but are not required to be reported on the eCRF during study treatment. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
- ^k Hematology includes CBC, with RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Hematologic evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).
- ^l Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).
- ^m All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV DNA must be collected on or before Cycle 1, Day 1, in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.
- ⁿ Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

Appendix 1 Schedule of Assessments (cont.)

- ^o All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test within 7 days prior to enrollment. During the treatment period, urine pregnancy test in women of childbearing potential in both treatment arms must be performed within 3 days prior study drug administration of every 3 cycles of protocol mandated therapy. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For patients who discontinue therapy before end of planned therapy, a pregnancy test must be done at the completion/early termination visit (approximately 28–42 days after the last dose of HER2-targeted therapy), and at 3 months and for HER2-targeted therapy, additionally at 6 months after the discontinuation of study treatment.
- ^p Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Radiologic imaging performed during the screening period should consist of 1) CT (with oral or IV contrast unless contraindicated) and/or MRI of the chest, abdomen, and pelvis, 2) bone scan or PET scan, 3) Brain MRI/CT and 4) any other imaging studies (CT of neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT of chest, abdomen, and pelvis performed during screening, then the patient should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study).
- Tumor assessments will be performed at baseline, every 6 weeks (± 7 days) following randomization, with additional scans as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of the following assessments every 6 weeks: 1) CT and/or MRI of the chest/abdomen/pelvis, as well as other known sites of disease, *including brain*, 2) If a patient has only bone as a site of involvement at screening which is determined to be measurable disease as per RECIST 1.1, then a bone scan or PET scan is mandated at each tumor assessment. Otherwise, a bone scan or PET scan is to be performed as clinically indicated, e.g., suspicion of disease progression, and 3) in cases where patients demonstrate control of their systemic disease but who newly develop isolated brain metastases and are eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments, *and* 4) any other imaging studies felt to be clinically indicated by the treating physician. Tumor response will be evaluated using RECIST v1.1 ([Appendix 4](#) and immune-modified RECIST [Appendix 5](#)). In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first. Results must be reviewed by the investigator before dosing at the next cycle.
- ^q An isotope bone scan and/or FDG PET will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

Appendix 1 Schedule of Assessments (cont.)

- ^r 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, or 3) if a patient demonstrates control of systemic disease but has a newly developed isolated brain metastases and is eligible to remain on study treatment, a brain MRI or CT will be performed along with regularly scheduled tumor assessments.
- ^s A 12-lead ECG is required at screening. Subsequent ECGs may be performed as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.
- ^t LVEF assessment by ECHO is preferred, but LVEF may also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.
- ^u Auto-antibody testing includes anti-nuclear antibody, anti-double-stranded DNA, and circulating and perinuclear cytoplasmic antibody. The baseline sample will be obtained pre-treatment Cycle 1, Day 1, before the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally.
- ^v At screening, the FFPE archival tumor block from the most recently collected, available tumor tissue or fresh core biopsy (3 cores) is mandated. If more than 1 FFPE blocks exists from different time points e.g. initial diagnosis vs. metastatic disease tissue, the most recent block is mandatory to be sent. If the FFPE block from the earlier timepoint is available then this would be requested to also be sent. In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided. 20-25 freshly cut, unstained slides will be acceptable in lieu of the FFPE block. Optional core biopsies will be obtained at Cycle 1, Day 1 and Cycle 2, Day 1 (± 3 days) if patient consented. At the study drug discontinuation/early study completion visit, if reason for discontinuation is disease progression, a biopsy must be taken (if deemed clinically feasible) before next line of therapy begins, unless purely anti-hormonal therapy.
- ^w Atezolizumab or placebo will be administered first by IV infusion at a dose of 1200 mg on Cycle 1, and on Day 1 of each 21-day cycle thereafter. For the first infusion of atezolizumab or placebo, vital signs should be determined within 60 minutes before, every 15 (± 5) minutes during, and 30 (± 10) minutes after the infusion, if clinically indicated. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.
- ^x Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Day 1 of Cycle 1, and on Day 1 of each 21-day cycle thereafter. For patients assigned to trastuzumab emtansine therapy, trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

Appendix 2

Schedule of Pharmacokinetic and Immunogenicity Samples

Table 1 Anti-Therapeutic Antibody and Pharmacokinetic Assessments for Atezolizumab¹

Visit	Timepoint	Sample Type ^a
Cycle 1, Day 1 and Cycle 4 Day 1	Pre-infusion ^b of atezolizumab or placebo	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab
Cycle 1, Day 1 and Cycle 4 Day 1	30 minutes (\pm 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 (\pm 3 days)	Pre-infusion ^b of atezolizumab or placebo	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab
Study treatment/early discontinuation visit	At any time during visit	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab
120 days (\pm 28 days) after treatment completion or discontinuation	At any time during visit	Serum sample for atezolizumab pharmacokinetics
		Serum sample for ATA to atezolizumab

ATA= anti-therapeutic antibody.

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

^b Within 24 hours prior to atezolizumab infusion.

Appendix 2 Schedule of Pharmacokinetic and Immunogenicity Samples (cont.)

Table 2 Anti-Therapeutic Antibody and Pharmacokinetic Assessments for Trastuzumab Emtansine¹

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

ATA=anti-therapeutic antibody.

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

^b Within 24 hours prior to Trastuzumab emtansine administration.

Appendix 3 Schedule of Biomarker Samples

Table 3 Blood Samples for Biomarker Analysis

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

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

Appendix 3 Schedule of Biomarker Samples (cont.)

Table 4 Tissue Sample for Biomarker Analysis

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

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1

The following is a modified excerpt from the original publication (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).

1. Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable 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 of:

10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray (CXR).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also paragraph below on “Baseline documentation of target and non-target lesions” for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) 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 lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local treatment require particular comment:

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

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 as 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 as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

“Cystic lesions” thought to represent cystic metastases can be considered as 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 treatment, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

2. Target lesions: Specifications by methods of measurements

Measurement of 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 never more than 4 weeks before the beginning of the treatment.

Method of assessment

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 diameter as 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 CXR, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on CXR may be considered measurable if they are clearly defined and surrounded by aerated lung.

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 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 IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without 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 (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised but will be dependent on the study design.

3. Tumor response evaluation

Assessment of overall tumor burden and measurable disease

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. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

Baseline documentation 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 in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded.

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be *reproducible in 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 which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which 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. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan 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 which is reported as being 20 mm \times 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 < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression” (see also “Special notes on assessment of progression of non-target disease”).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Special notes on the assessment of target lesions

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 nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target lesions that become “too small to measure”: while on study, all lesions (nodal and non-nodal) 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 which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being “too small to measure.” When this occurs it is important that a value be recorded on the Case Report Form:

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 too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) 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

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: when non-nodal lesions “fragment,” the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining 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 maximal longest diameter for the “coalesced lesion.”

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions (and, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Special notes on assessment of progression of non-target disease

When the patient also has measurable disease: **in this setting, to achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of treatment.** 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 disease in the face of SD or PR of target disease will therefore be extremely rare.

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

When the patient has only non-measurable disease: this circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in “volume” (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large,” an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “**sufficient to require a change in treatment.**” If “unequivocal progression” is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

New lesions

The appearance of new malignant lesions denotes PD; 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: i.e., 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 PD.

If a new lesion is equivocal, for example because of its small size, continued treatment and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Appendix 4 Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

Evaluation of response

Timepoint Response (Overall response)

It is assumed that at each protocol specified timepoint, a response assessment occurs.

[Table 1](#) provides a summary of the overall response status calculation at each timepoint.

When patients have non-measurable (therefore non-target) disease only, [Table 2](#) is to be used.

Table 1: Timepoint Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not Evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

Table 2: Timepoint Response

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not Evaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response; PD=progressive disease; SD=stable disease.

* “Non-CR/non-PD” is preferred over “stable disease” for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point 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.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be “Unable to Assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as ‘not assessed’, the response for non-target lesions should be “Unable to Assess” (except where there is clear progression). Overall response would be “Unable to Assess” if either the target response or the non-target response is “Unable to Assess” (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

Table 3: Best Overall Response when Confirmation is required

Overall response First time point	Overall response Subsequent time point	BEST Overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	Not Evaluable	SD provided minimum criteria for SD duration met, otherwise Not Evaluable
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	Not Evaluable	SD provided minimum criteria for SD duration met, otherwise Not Evaluable
Not Evaluable	Not Evaluable	Not Evaluable

CR= complete response; PD=progressive disease; PR=partial response; SD= stable disease.

* If a CR is truly met at first time point then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes “CR” may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR not CR at the first time point. Under these circumstances the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to

Appendix 4

Response Evaluation Criteria in Solid Tumors, Version 1.1 (cont.)

overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of “zero” on the eCRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD 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 disease as shown in [Tables 1–3](#).

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.

In studies where patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed that account for the possible appearance of new lesions.

Immune-modified RECIST is derived from RECIST, Version 1.1 (v1.1) conventions and immune-related response criteria (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Immune-Modified RECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	Immune-Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added to the total tumor burden calculation (?) and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of $\geq 20\%$ increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST = Response Evaluation Criteria in Solid Tumors.

A. DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression.

A.1 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 CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

A.2 NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 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 lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

A.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, PET scan, or 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 as 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 as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

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.

B. TUMOR RESPONSE EVALUATION

B.1 DEFINITIONS OF TARGET/NON-TARGET LESIONS

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 recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and 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. Nodal 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 mm \times 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

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

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.

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

Non-Target Lesions

All other lesions (or sites of disease), 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 eCRF (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of CR (i.e., a CR is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non-lymph node lesions must be ≥ 10 mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all new lesions with measurements obtained at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

B.2 CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest axis for non-nodal lesions, short axis for nodal lesions) of all target lesions will be calculated as a measure of tumor burden.

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at On-Study Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of immune-modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion ≥ 15 mm, it will be considered a measurable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of < 10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter ≥ 15 mm).

The appearance of new lymph nodes with diameter < 10 mm should not be considered pathological and not considered a new lesion.

B.3 RESPONSE CRITERIA

Timepoint Response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. [Table 1](#) provides a summary of the overall response status calculation at each timepoint.

CR: Disappearance of all target and non-target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

PR: At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: The appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Immune-Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular assessment timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Appendix 5 Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

Table 1 Immune-Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters ^a	Non-Target Lesion Response Assessment	Overall Immune-Modified RECIST Timepoint Response
– 100% from baseline ^b	CR	CR
– 100% from baseline ^b	Non-CR or not all evaluated	PR
≤ – 30% from baseline	Any	PR
> – 30% to < + 20%	Any	SD
Not all evaluated	Any	NE
≥ + 20% from nadir SLD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of the longest diameter.

^a Percent change in sum of the diameters (including measurable new lesions when present).

^b When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Appendix 5

Immune-Modified Response Evaluation Criteria in Solid Tumors (cont.)

REFERENCES

- 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.
- 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.
- 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.
- 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 Unidimensional measurements. *Clin Cancer Res*. 2013;14:3936–43.

Appendix 6 Ventana HER2 IHC Assay

The PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody (PATHWAYHER2 [4B5]) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of HER2 antigen in sections of formalin-fixed, paraffin-embedded breast cancer tissue to determine tumor HER2 immunohistochemistry (IHC) status and to select HER2-positive patients for enrollment in study WO30085. The 4B5 IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to ado-trastuzumab emtansine and will be used for investigational purposes only.

Device Description

The PATHWAY HER2 (4B5) IHC assay is an automated immunohistochemical staining assay system comprising a pre-dilute, ready-to-use, rabbit monoclonal primary antibody(clone 4B5) directed against the internal domain of HER2, the BenchMark ULTRA automated slide staining platform, and ultraView universal DAB detection kit. The reagents and the IHC procedure are optimized for use on the BenchMark ULTRA automated slide stainer, utilizing VSS software (Ventana System Software). Details of the staining protocol and scoring criteria can be found in instruction for use and interpretation guide published by Ventana.

Appendix 7 Ventana HER2 ISH Assay

Probe Cocktail is intended to determine the ratio of the HER2 gene to chromosome 17 using two-color chromogenic in situ hybridization (ISH) in formalin-fixed, paraffin-embedded human breast cancer tissue to determine tumor HER2 gene status and select HER2-positive patients for enrollment in study BO28407. The INFORMHER2 Dual ISH DNA Probe Cocktail is currently being developed by Ventana Medical Systems as a companion diagnostic to ado-trastuzumab emtansine and will be used for investigational purposes only for Study WO30085.

The Ventana INFORM HER2 Dual ISH assay consists of a dinitrophenyl (DNP)-labeled double stranded probe that targets the HER2 gene region of chromosome 17 and a digoxigenin (DIG)-labeled double stranded probe that hybridizes to repetitive sequences in the centromeric region of chromosome 17 (INFORM Chromosome 17 probe). The probes are packaged as a mixture and require the use of Ventana's ultraView™ SISHDNP Detection Kit, ultraView Red DIG Detection Kit, and other accessory reagents to stain routinely processed, FFPE tissue sections on Ventana automated slide stainer instruments.

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 even 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 Preexisting Autoimmune Diseases

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 subjects with a medical history of such entities as atopic disease or childhood arthralgias for which 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). Contact the Medical Monitor regarding any uncertainty about autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Interstitial cystitis
Addison's disease	Kawasaki disease
Ankylosing spondylitis	Lambert-Eaton myasthenia syndrome
Antiphospholipid antibody syndrome	Lupus erythematosus
Aplastic anemia	Lyme disease, chronic
Autoimmune hemolytic anemia	Meniere syndrome
Autoimmune hepatitis	Mooren ulcer
Autoimmune hypoparathyroidism	Morphea
Autoimmune hypophysitis	Multiple sclerosis
Autoimmune myocarditis	Myasthenia gravis
Autoimmune myositis	Neuromyotonia
Autoimmune oophoritis	Opsoclonus myoclonus syndrome
Autoimmune orchitis	Optic neuritis
Autoimmune thrombocytopenic purpura	Ord thyroiditis
Behçet disease	Pemphigus
Bullous pemphigoid	Pernicious anemia
Chronic fatigue syndrome	Polyarteritis nodosa
Chronic inflammatory demyelinating polyneuropathy	Polyarthrits
Chung-Strauss syndrome	Polyglandular autoimmune syndrome
Crohn disease	Primary biliary cirrhosis
Dermatomyositis	Psoriasis
Diabetes mellitus, type 1	Reiter syndrome
Dysautonomia	Rheumatoid arthritis
Epidermolysis bullosa acqvista	Sarcoidosis
Gestational pemphigoid	Scleroderma
Giant cell arteritis	Sjögren syndrome
Goodpasture syndrome	Stiff-Person syndrome
Glomerulonephritis	Takayasu arteritis
Graves disease	Ulcerative colitis
Guillain-Barré syndrome	Vasculitis
Hashimoto disease	Vitiligo
IgA nephropathy	Vogt-Kovanagi-Harada disease
Inflammatory bowel disease	Wegener granulomatosis

Appendix 11 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.