**Official Title:** A Phase III, Multicenter, Randomized, Open-Label Study Comparing Atezolizumab (Anti-Pd-L1 Antibody) in Combination With Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone in Patients With Operable Triple-Negative Breast Cancer

**NCT Number:** NCT03498716

**Document Date:** Protocol Version 9: 01-Mar-2023

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY COMPARING ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ADJUVANT ANTHRACYCLINE/TAXANE-BASED CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE IN PATIENTS WITH OPERABLE TRIPLE-NEGATIVE BREAST CANCER** |
| **PROTOCOL NUMBER:** | BIG 16-05/AFT-27/WO39391 |
| **VERSION NUMBER:** | 9 |
| **EUDRACT NUMBER:** | 2016-003695-47 |
| **IND NUMBER:** | 123277 |
| **NCT NUMBER:** | NCT03498716 |
| **TEST PRODUCT:** | Atezolizumab (RO5541267) |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **ACADEMIC PARTNERS:** | Breast International Group (BIG)<br>Alliance Foundation Trials (AFT)<br>Institut Jules Bordet/Clinical Trials Support Unit (IJB/CTSU)<br>Frontier Science Foundation |
| **APPROVAL DATE:** | See electronic signature and date stamp on the final page of this document. |

## PROTOCOL HISTORY

| Protocol | | Associated Country Specific Protocols | | |
|---|---|---|---|---|
| **Version** | **Date Final** | **Country** | **Version** | **Date Final** |
| 9 | See electronic date stamp on the final page of this document. | — | — | — |
| 8 | 24 November 2021 | — | — | — |
| 7 | 17 February 2021 | — | — | — |
| 6 | 14 February 2020 | VHP | 6 | 22 April 2020 |
| — | — | France | 5 | 12 Nov 2019 |
| 4 | 15 November 2018 | China | 4 | 19 June 2019 |
| 3 | 30 May 2018 | France | 3 | 13 November 2018 |
| 2 | 2 November 2017 | VHP | 2 | 19 January 2018 |
| 1 | 26 July 2017 | — | — | — |

## PROTOCOL AMENDMENT, VERSION 9:
## RATIONALE

Protocol BIG 16-05/AFT-27/WO39391 has been amended in a response to a Health Authority's request to conduct a formal interim analysis to determine the ability of the study to provide an acceptable benefit-risk assessment upon trial conclusion.

- Sections 3.1.1, 6.1, and 6.9.1 have been updated to align with the methods and analyses described in the statistical analysis plan.

To align with the Atezolizumab Investigator's Brochure, Version 19, and the associated Addendums 1 and 2, the following changes have been made:

- The list of identified risks for atezolizumab has been revised to include pericardial disorders, myelitis, and facial paresis (Section 5.1.1, Appendix 9).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab, and language has been revised accordingly (Section 5.1.1).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
- Appendix 6 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent andto include autoimmune myelitis in the table.
- The guidelines for the management of adverse events have been updated (Appendix 9).

Additional minor changes have been made to improve clarity and consistency including the following:

- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.6.11.5).
- Text has also been added to indicate that the VENTANA PD-L1 (SP142) Assay may be considered investigational per local regulations (Section 4.6.7).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 8.4).
- Management guidelines for Grade 4 hypophysitis have been added to correct an inadvertent omission in the previous version (Appendix 9, Table 4).

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES



## LIST OF APPENDICES

## PROTOCOL AMENDMENT ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY COMPARING ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ADJUVANT ANTHRACYCLINE/TAXANE-BASED CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE IN PATIENTS WITH OPERABLE TRIPLE-NEGATIVE BREAST CANCER** |
| **PROTOCOL NUMBER:** | BIG 16-05/AFT-27/WO39391 |
| **VERSION NUMBER:** | 9 |
| **EUDRACT NUMBER:** | 2016-003695-47 |
| **IND NUMBER:** | 123277 |
| **NCT NUMBER:** | NCT03498716 |
| **TEST PRODUCT:** | Atezolizumab (RO5541267) |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **ACADEMIC PARTNERS:** | Breast International Group (BIG)<br>Alliance Foundation Trials (AFT)<br>Institut Jules Bordet/Clinical Trials Support Unit (IJB/CTSU)<br>Frontier Science Foundation |

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of this form to the Sponsor or its designee. Contact details will be provided to the investigator prior to study start.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY COMPARING ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH ADJUVANT ANTHRACYCLINE/TAXANE-BASED CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE IN PATIENTS WITH OPERABLE TRIPLE-NEGATIVE BREAST CANCER** |
| **PROTOCOL NUMBER:** | BIG 16-05/AFT-27/WO39391 |
| **VERSION NUMBER:** | 9 |
| **EUDRACT NUMBER:** | 2016-003695-47 |
| **IND NUMBER:** | 123277 |
| **NCT NUMBER:** | NCT03498716 |
| **TEST PRODUCT:** | Atezolizumab (RO5541267) |
| **PHASE:** | III |
| **INDICATION:** | Triple-negative breast cancer |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **ACADEMIC PARTNERS:** | Breast International Group (BIG)<br>Alliance Foundation Trials (AFT)<br>Institut Jules Bordet/Clinical Trials Support Unit (IJB/CTSU)<br>Frontier Science Foundation |

### OBJECTIVES AND ENDPOINTS

This study (Study BIG 16-05/AFT-27/WO39391, also known as ALEXANDRA/IMpassion030) will evaluate the efficacy, safety, and pharmacokinetics of adjuvant atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (referred to as atezolizumab + T-AC/EC) compared with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (referred to as T-AC/EC) in patients with Stage II-III triple-negative breast cancer (TNBC). Specific objectives and corresponding endpoints for the study are outlined below.

| Objectives | Corresponding Endpoints |
|---|---|
| **Primary Efficacy Objective:** | |
| • To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with TNBC | • iDFS, defined as the time from randomization until the date of the first occurrence of one of the following events:<br>– Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion) |

| Objectives | Corresponding Endpoints |
|---|---|
| • **Primary Efficacy Objective (cont.):** | |
| | – Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)<br>– Ipsilateral second primary invasive breast cancer<br>– Contralateral invasive breast cancer<br>– Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the sites mentioned above]) that has either been histologically confirmed and/or clinically/radiographically diagnosed as recurrent invasive breast cancer<br>– Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause |
| **Secondary Efficacy Objectives:** | |
| • To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone | • iDFS in the subpopulation with PD-L1-selected tumor status (IC1/2/3)<br>• iDFS in the subpopulation with node-positive disease<br>• OS, defined as the time from randomization to death from any cause<br>• iDFS defined the same way as the primary endpoint but including second primary non-breast invasive cancer (except for non-melanoma skin cancers and in situ carcinoma of any site) as an event<br>• RFI, defined as the time from randomization until local, regional, or distant disease recurrence<br>• Distant RFI, defined as the time from randomization until distant disease recurrence only<br>• DFS, defined as the time from randomization to the first occurrence of disease recurrence or death from any cause.<br>• Events defining DFS:<br>– Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)<br>– Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast) |

| Objectives | Corresponding Endpoints |
|---|---|
| **Secondary Efficacy Objectives (cont.):** | |
| | – Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the sites mentioned above]) that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer<br>– Contralateral invasive breast cancer<br>– Ipsilateral or contralateral DCIS<br>– Second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinoma of any site)<br>– Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified it at all possible |
| • To evaluate PROs of function and HRQoL associated with atezolizumab + T-AC/EC compared with T-AC/EC alone, as measured by the functional and HRQoL- scales of the EORTC QLQ-C30 | • Mean and mean changes from baseline score in function (role, physical) and GHS/HRQoL by assessment timepoint, and between treatment arms as assessed by the functional and GHS/HRQoL scales of the EORTC QLQ-C30 |
| **Exploratory Efficacy Objectives:** | |
| • To evaluate PROs of disease/treatment-related symptoms associated with atezolizumab + T-AC/EC compared with T-AC/EC alone, as measured by the EORTC QLQ-C30 | • Mean and mean changes from baseline score in disease/treatment-related symptoms by assessment timepoint, and between treatment arms as assessed by all symptom items/scales of the EORTC QLQ-C30 |
| • To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to T-AC/EC compared with T-AC/EC alone, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical well-being subscale of the FACT-G quality-of-life instrument | • Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G |
| • To evaluate patient's health utility as measured by the EQ-5D-5L questionnaire to generate utility scores for use in economic models for reimbursement | • Utility scores of the EQ-5D-5L questionnaire |
| **Safety Objective:** | |
| • To evaluate the safety and tolerability of atezolizumab + T-AC/EC compared with T-AC/EC alone | • Occurrence and severity of adverse events as defined by NCI CTCAE v5.0 |
| **Pharmacokinetic Objective:** | |
| • To characterize the serum pharmacokinetics of atezolizumab when administered in combination with T-AC/EC chemotherapy | • Serum concentration of atezolizumab at specified timepoints |

| Objectives | Corresponding Endpoints |
|---|---|
| **Immunogenicity Objective:** | |
| • To evaluate the immune response to atezolizumab | • Incidence of ADAs during the study relative to the prevalence of ADAs at baseline |
| **Exploratory Immunogenicity Objective:** | |
| • To evaluate potential effects of ADAs | • Relationship between ADA status and efficacy, safety, or PK endpoints |
| **Exploratory Biomarker Objective** | |
| • To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in tumor tissue and blood and their association with efficacy endpoints including, but not limited to, disease recurrence | • Relationship between tumor derived RNA-based immune and tumor gene signatures and efficacy endpoints including, but not limited to, the primary endpoint (iDFS)<br>• Relationship between tumor-based TILs and/or CD8 IHC and efficacy endpoints including, but not limited to, the primary endpoint (iDFS) |
| • To identify biomarkers that are associated with resistance to atezolizumab in combination with T-AC/EC or can increase the knowledge and understanding of disease biology | • Relationship between biomarkers in blood and tumor tissue between pretreatment and post-recurrence samples collected at disease recurrence. These biomarkers may include, and are not limited to, the following:<br>– Acquired mutations assessed using DNA NGS<br>– Changes in the tumor immune microenvironment and biology as assessed by RNA profiling and IHC |

ADA = anti-drug antibodies; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQoL 5 Dimension, 5 Level; FACT-G = Functional Assessment of Cancer Therapy-General; GHS = global health status; HRQoL = health-related quality of life; IC = tumor-infiltrating immune cell, iDFS = invasive disease-free survival; IHC = immunohistochemistry; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NGS = next-generation sequencing; OS = overall survival; PK = pharmacokinetic; PRO = patient-reported outcomes; QLQ-C30 = Quality of Life Questionnaire-Core 30; RFI = recurrence-free interval; T-AC/EC = paclitaxel, dose-dense doxorubicin/epirubicin, and cyclophosphamide; TILs = tumor-infiltrating lymphocyte; TNBC = triple-negative breast cancer.

## STUDY DESIGN

### DESCRIPTION OF STUDY

This is a global Phase III, open-label, randomized, controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of adjuvant treatment with atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with newly diagnosed TNBC who have completed surgery with curative intent of their primary tumor and are candidates for adjuvant systemic therapy following surgery.

The HER2 and ER/PgR status will be used to define TNBC. The HER2 negativity will be defined by central laboratory assessment using in situ hybridization (ISH) or immunohistochemistry (IHC) assays per the criteria outlined in the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for HER2 testing. ER/PgR negativity will be defined by central laboratory assessment using IHC assays per the criteria outlined in the ASCO/CAP guidelines for ER/PgR testing. Central laboratory assessment will occur prior to randomization. Patients whose tumors are not confirmed to be triple negative by central laboratory assessment will not be eligible. The PD-L1 status will be assessed by central laboratory. Patients whose tumor tissue is not evaluable for PD-L1 will not be eligible. All site and study team staff will be blinded to PD-L1 status.

Patients who provide informed consent and are eligible will be randomized in a 1:1 ratio to receive either of the following treatment regimens:

- **Arm A**: Atezolizumab and Chemotherapy
  - Atezolizumab: atezolizumab (840 mg) administered via IV Q2W in combination with chemotherapy (as described below), followed by atezolizumab maintenance therapy (1200 mg IV infusion every 3 weeks [Q3W]) to complete a total duration of 1 year of atezolizumab treatment from the first administration of atezolizumab.
  - Chemotherapy: paclitaxel (80 mg/m2) administered via IV infusion weekly (QW) for 12 weeks followed by dose-dense doxorubicin (60 mg/m2) or dose-dense epirubicin (90 mg/m2) IV (investigator's choice)+cyclophosphamide (600 mg/m2) IV repeated Q2W for 4 doses.
  - Granulocyte colony-stimulating factor (G-CSF) (e.g., filgrastim or pegfilgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF) treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, European Organisation for Research and Treatment of Cancer (EORTC), or European Society for Medical Oncology (ESMO) guidelines or per local standard practice.
- **Arm B**: Chemotherapy alone
  - Paclitaxel (80 mg/m2) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m2) or dose-dense epirubicin (90 mg/m2) IV (investigator's choice)+cyclophosphamide (600 mg/m2) IV repeated Q2W for 4 doses.
  - Granulocyte colony-stimulating factor (e.g., filgrastim or pegfilgrastim) or GM-CSF treatment is permitted for patients receiving chemotherapy and is required during the dose dense doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, EORTC, or ESMO guidelines or per local standard practice.

The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of patients with node-negative disease.

Patients who do not initially meet all eligibility criteria, other than TNBC status, may be re-screened once.

Randomization will be stratified by the following factors:

- Axillary nodal status (0 vs. 1–3 vs. $\geq$ 4 positive lymph nodes)
- Surgery (breast conserving vs. mastectomy)
- Tumor PD-L1 status (tumor-infiltrating immune cell [IC] 0 vs. IC1/2/3)

Randomization should occur no more than 8 weeks (56 days) after definitive surgery, and study drug administration should begin within 1 week (7 days) after randomization but no sooner than 2 weeks (14 days) after last surgery. In case of multiple surgeries performed for the breast cancer treatment, this time period should count starting from the last performed curative surgery.

To ensure comparability of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will undergo similar assessments as patients in Arm A. These assessments will consist of formal clinic visits for evaluation of symptoms and adverse events, including cardiac toxicity. Following the induction period, patients in Arm B will continue PRO assessments, laboratory evaluations, left ventricular ejection fraction (LVEF) monitoring, and limited physical examinations on a regular basis for the first year after randomization. For patients in both arms, patient-reported outcome (PRO) assessments, LVEF monitoring, physical examinations and other assessments will continue at a reduced frequency after the first year after randomization.

Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

In case of unacceptable toxicity attributed to chemotherapy in Arm A, atezolizumab should be stopped and restarted together with chemotherapy if there is no contraindication. In cases where chemotherapy is permanently discontinued, atezolizumab may be restarted if there is no contraindication and should be based on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed. In case of toxicities attributed to atezolizumab, chemotherapy may be continued independently of atezolizumab if there is no contraindication. Atezolizumab may be restarted when the conditions for retreatment have been met. When atezolizumab is restarted, the infusions should remain synchronized and aligned with the chemotherapy schedule and it should be administered at a scheduled atezolizumab visit (i.e., missed doses of atezolizumab will not be made up).

Dose delay and modification guidelines for chemotherapy are provided in the protocol. Management guidelines for toxicities associated with atezolizumab are provided in the protocol.

Treatment will be discontinued in the event of disease recurrence, unacceptable toxicity/adverse event occurrence, pregnancy, withdrawal of consent, significant protocol violations, or study termination. Patients who prematurely discontinue from the study will not be replaced. Except for patients who withdraw consent from study follow-up, those who have prematurely discontinued from treatment will be followed for safety (including cardiac toxicity) and efficacy endpoints.

Efficacy, safety, laboratory, PROs, pharmacokinetic (PK) measures, and biomarkers will be assessed throughout the study. Following completion of study treatment, all patients will continue to be followed for efficacy, safety, and PRO objectives until the end of the study.

Safety assessments will include the occurrence and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). The LVEF will be assessed serially by echocardiogram (ECHO)/multiple-gated acquisition (MUGA) scans. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including tumor tissues, as well as plasma and blood, will be collected for exploratory biomarker assessments.

An Independent Data Monitoring Committee (IDMC) will evaluate safety and efficacy data during the study. No IDMC member may participate in the Study as an investigator, co-investigator, sub-investigator, committee member (other than IDMC), or patient, or in any other capacity that might compromise his or her independence and privileged activities within the IDMC. In order to ensure independence, members should have no involvement in the design and conduct of the Study except through their role on the IDMC and have no financial or other interests in the sponsor's business or other Study organizers (BIG, AFT, FS, IJB) that could influence (or be perceived to influence) their objectivity in evaluating Study data. The IDMC will follow a charter that outlines the IDMC roles and responsibilities.

**NUMBER OF PATIENTS**

Approximately 2300 patients will be enrolled in this study at approximately 370–450 sites globally. It is estimated that the study will enroll patients over approximately 4 years.

**TARGET POPULATION**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability to comply with protocol, in the investigator's judgment
- Women or men aged ≥ 18 years at time of signing ICF
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Non-metastatic operable Stage II-III breast cancer
  - Patients with node-negative disease must have a pathological tumor size > 2 cm. Patients with node-negative multifocal, multicentric- or bilateral breast cancer are eligible providing that at least one lesion is > 2 cm in size.

- Histologically documented TNBC (negative HER2, ER, and PgR status)
  - HER2 negativity will be defined by central laboratory assessment using ISH or IHC assays per ASCO/CAP criteria and ER/PgR negativity will be defined by central laboratory assessment using IHC per ASCO/CAP criteria. Central laboratory assessment will occur prior to randomization.
  - Patients with multifocal invasive tumors (more than one tumor confined to the same quadrant as the primary tumor) or multicentric invasive tumors (more than one tumor in different quadrants of the same breast) are eligible provided all discrete lesions are sampled and centrally confirmed as TNBC. Patients with non-TNBC invasive components are not eligible to participate in this study.
- Confirmed tumor PD-L1 evaluation as documented through central testing of a representative tumor tissue specimen
- Adequately excised: Patients must have undergone either breast-conserving surgery or mastectomy/nipple- or skin-sparing mastectomy.
  - For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. In cases in which the patient underwent breast-conserving surgery and there was a microscopic positive deep margin (with no other positive margins), if the tumor was resected up to the chest wall muscle and the surgeon considers that a mastectomy will not provide a negative deep margin, the patient does not need to undergo a mastectomy in order to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.
  - For patients who undergo mastectomy/nipple- or skin-sparing mastectomy, margins must be free of gross residual tumor. It is recommended that patients should have a negative microscopic margin in accordance with local pathology protocol. Patients with a microscopic positive deep margin are eligible.
- Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 8th edition): Patient must have had sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND) for evaluation of pathologic nodal status.
  - Axillary nodal dissection(s) should yield a total of at least six nodes (including the axillary lymph nodes resected at the SLNB plus the lymph nodes collected at the axillary nodal dissection).
  - Patients with positive SLNB should undergo axillary dissection unless all of the following characteristics apply:

    No palpable nodes

    No more than 2 pathologically positive lymph nodes

    Breast-conserving surgery has been completed with tangential whole breast irradiation planned OR mastectomy with regional nodal radiotherapy planned.

    Clinical tumor size $\leq$ T2 (5 cm)
  - In the case that all of the above are applicable, it is not mandatory to have the axillary dissection but it is left at the discretion of the investigator as per site standard practice.
  - In the case of subjects with tumors >2cm and regional lymph node found to have micrometastases or isolated tumor cells: Pathological classification of regional lymph node micrometastases (tumor deposits $>$ 0.2 mm and $\leq$ 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0.

    The study population will be enriched for patients with node-positive disease such that the final population will contain at least 50% node-positive patients.

- Patients with synchronous bilateral invasive disease are eligible only if all bilateral invasive lesions are histologically confirmed as triple negative by central laboratory and have completed adequate pathological tumor-node metastasis staging bilaterally as described above.
- No more than 8 weeks (56 days) may elapse between definitive breast surgery (or the last surgery with curative intent if additional resection is required for breast cancer) and randomization.
- Baseline LVEF $\geq$ 53% measured by ECHO (preferred) or MUGA scans
  - Baseline LVEF to be conducted within 28 days prior to randomization.
- Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 28 days prior to randomization:
  - Absolute neutrophil count (ANC) $\geq$ 1500 cells/$\mu$L (without G-CSF support within 2 weeks prior to Cycle 1, Day 1)
  - Lymphocyte count $\geq$ 500 cells/$\mu$L
  - Platelet count $\geq$ 100,000 cells/$\mu$L (without transfusion within 2 weeks prior to Cycle 1, Day 1)
  - Hemoglobin $\geq$ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ the upper limit of normal (ULN)
  - Serum total bilirubin $\leq 1.0 \times$ ULN

    Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN within 28 days prior to randomization
  - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding randomization
  - Creatinine clearance $\geq$ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin $\geq$ 2.5 g/dL
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening
  - The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
  - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Representative formalin-fixed, paraffin embedded (FFPE) tumor specimen from surgical resection in paraffin blocks (preferred) or approximately 25 unstained slides (minimum of 20 slides), with an associated pathology report documenting locally assessed ER, PgR, and HER2 negativity.
  - Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated centrally for PD-L1 expression prior to enrollment. Fine-needle aspiration, brushing, cell pellet from cytology specimens are not acceptable. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible.
  - If multiple tumor specimens are submitted, 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.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab, or 6 months after the last dose of paclitaxel or doxorubicin/epirubicin, or 12 months after the last dose of cyclophosphamide, whichever is later. Women must refrain from donating eggs during the same period.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate 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 6 months after the last dose of paclitaxel, or doxorubicin/epirubicin or 12 months after the last dose of cyclophosphamide, whichever is later. 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 6 months after the last dose of paclitaxel, or doxorubicin/epirubicin or 12 months after the last dose of cyclophosphamide, whichever is later 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 adequate methods of contraception.
- Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) and have not undergone a sterilization procedure must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires

Exclusion Criteria

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

- Prior history of invasive breast cancer
- Any T4 tumor as defined by tumor-node metastasis classification in UICC/AJCC, 8th edition, including inflammatory breast cancer
- For the currently diagnosed breast cancer, any previous systemic anti-cancer treatment (e.g., neoadjuvant or adjuvant), including, but not limited to, chemotherapy, anti-HER2 therapy (e.g., trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib, or other tyrosine kinase inhibitors), hormonal therapy, or anti-cancer RT other than planned in the context of this study
- Previous therapy with anthracyclines or taxanes for any malignancy
- History of DCIS and/or LCIS that was treated with any form of systemic, hormonal therapy, or RT to the ipsilateral breast where invasive cancer subsequently developed

  - Patients who had their DCIS/LCIS treated only with surgery and/or contralateral DCIS treated with RT are allowed to enter the study.
- Contraindication to RT when adjuvant RT is clinically indicated
- Cardiopulmonary and/or cerebrovascular dysfunction as defined by any of the following prior to randomization
  - History of NCI CTCAE (v5.0) Grade $\geq$ 2 symptomatic congestive heart failure or New York Heart Association (NYHA) Class $\geq$ II
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second degree AV-block Type 2 Mobitz 2, or third-degree AV-block])
  - Significant symptoms (Grade $\geq$ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to randomization
  - Uncontrolled hypertension (systolic blood pressure $>$ 160 mmHg and/or diastolic blood pressure $>$ 100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
  - Cerebrovascular ischemic event (e.g., ischemic within 12 months prior to randomization)
- Prior malignancies within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (i.e., adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the paclitaxel (e.g., polyoxyl 35 castor oil), cyclophosphamide, or doxorubicin/epirubicin formulations
- Known allergy or hypersensitivity to G-CSF or GM-CSF formulations
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.
  - Patients with controlled Type I diabetes mellitus who are on an insulin regimen may be eligible for this study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all the following conditions are met:

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

    Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Current treatment with anti-viral therapy for HBV
- Urinary outflow obstruction
- Active tuberculosis
- Severe infections within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during study treatment
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study or within 5 months after the last dose of atezolizumab
  - Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to initiation of study treatment, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists or immune checkpoint-blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] alpha agents) within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication during the study
  - 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 based on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
- Pregnant or lactating, or intending to become pregnant during the study
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease
- Under any legal protection (tutorship/curatorship).

**END OF STUDY**

The study is planned to end after approximately *299 deaths* have been observed for the analysis of OS.

**LENGTH OF STUDY**

The total duration of the study is expected to be approximately 7 years after the first patient is randomized.

## INVESTIGATIONAL MEDICINAL PRODUCTS

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

**ATEZOLIZUMAB (ARM A ONLY)**

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg Q2W (14 [± 3] days) in combination with T-AC/EC chemotherapy. Upon completion of chemotherapy, atezolizumab will be continued as maintenance therapy at a dose of 1200 mg administered by IV infusion Q3W (21 [± 3] days) to complete 1 year of treatment (i.e., approximately 1 year total duration of atezolizumab therapy from first administration of atezolizumab).

**BACKGROUND TREATMENT**

Patients will receive paclitaxel (80 mg/m$^2$) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m$^2$) or dose-dense epirubicin (90 mg/m$^2$) IV (investigator's choice) + cyclophosphamide (600 mg/m$^2$) administered via IV infusion Q2W with G-CSF/GM-CSF support for 4 cycles (i.e., a total of 4 doses of doxorubicin/epirubicin and cyclophosphamide).

## STATISTICAL METHODS

**PRIMARY ANALYSIS**

The primary efficacy variable is invasive disease-free survival (iDFS), defined as the time between randomization and date of first occurrence of an iDFS event as described in the protocol. Data from patients who have not had an event at the time of data analysis will be censored on the date on which they are last known to be alive and event free, on or before the clinical data cutoff date of the respective analysis.

Patients with no postbaseline information will be censored on the date of randomization.

The log-rank test, stratified by the protocol-defined stratification factors, will be used to compare iDFS between the two treatment arms. The hazard ratio (HR) for iDFS will be estimated with use of a stratified Cox proportional hazards model. The Kaplan-Meier approach will be used to estimate 3-year iDFS rates, and corresponding 95% Cis for each treatment arm will be used to describe iDFS in addition to the HR.

**DETERMINATION OF SAMPLE SIZE**

The final analysis of the primary endpoint of iDFS will take place when approximately *390 iDFS events* (approximately *17% of the planned enrollment* of 2300 patients experiencing an iDFS event) have occurred in the intent-to-treat (ITT) population. This sample size is computed on the basis of the following assumptions:

- Primary statistical test: two-sided, stratified log-rank test at the 0.05 significance level in the ITT population
- Approximately 80% power for iDFS
- A HR of 0.75
- Annual hazard rates of 0.047, 0.108, 0.035, 0.038, 0.029, and 0.014 in Years 1, 2, 3, 4, 5–6, and 7 and thereafter are assumed for the T-AC/EC arm based on the adjuvant TNBC trials ECOG E1199, BEATRICE, and IBCSG 22-00
- Based on the piecewise hazard rates given above for the control arm, and the assumed HR of 0.75 (thus reducing the risk of an iDFS event by 25% at each piecewise interval), the 3 year iDFS rate (probability of not having any iDFS event in the first 3 years) will be 82.7% in the T-AC/EC arm and 86.7% in the -atezolizumab + T-AC/EC arm

- 2.5% annual loss to follow-up for iDFS
- *Interim analyses* for iDFS in the ITT population (see below)

Accrual is projected to occur over 51 months. The required number of iDFS events *for the final analysis* in the ITT population is projected to occur *77 months* after first patient in. Also, on the basis of these assumptions, an observed HR of 0.81 or better will result in a statistically significant difference between the treatment arms (i.e., HR = 0.81 will be the minimally detectable difference for the analysis; this corresponds to an improvement in 3-year iDFS from 82.7% in the T-AC/EC arm to 85.7% in the atezolizumab + T-AC/EC arm).

The study duration for the secondary endpoint, OS, was determined on the basis of the number of events required to demonstrate efficacy with regard to OS. A total of *approximately 299 deaths* are required to achieve 80% power at a two-sided alpha level of 5% to detect an HR of 0.72, corresponding to an improvement in 5-year OS rate from 84% in the T-AC/EC arm to 88.2% in the atezolizumab + T-AC/EC arm assuming a constant hazard. An annual loss to follow-up of 2.5% and *three* interim analyses of OS are assumed. The final analysis of OS is planned to take place approximately 7 years after the first patient has been randomized.

**INTERIM ANALYSES**

*In a response to a Health Authority's request, a formal interim analysis will be conducted in mid-March 2023 to determine the ability of the study to provide an acceptable benefit-risk assessment upon trial conclusion. This interim analysis will include both assessment of efficacy and futility for iDFS based on the available efficacy (approximately 62% of the total iDFS events) and safety data. To control the Type I error in multiple efficacy analyses of iDFS, the interim and final efficacy analyses boundaries for statistical significance will be determined based on the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary. For the first interim analysis, statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $\leq 0.0088$ (observed HR $\leq 0.71$); a non-binding futility boundary is set at the iDFS hazard ratio of 1, thus futility can be declared if the observed iDFS HR at the first interim analysis is greater than 1.*

*The second* interim efficacy analysis of iDFS will be performed when approximately 80% of the total planned number of iDFS events have occurred. On the basis of the assumption presented above, it is projected that 80% (312) iDFS events will have been observed approximately 59 months after the first patient randomized.

*For the second interim efficacy analysis* of iDFS, statistical significance will be determined based on the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary. Statistical significance will be declared if the p-value from the two-sided stratified log-rank test *is* $\leq 0.0218$ (observed HR $\leq 0.77$) depending on the actually observed number of events. If the null hypothesis for iDFS is not rejected at the interim analysis and the study continues, the final analysis of iDFS will be performed when approximately 388 iDFS events have occurred; statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $p \leq 0.0422$ (observed HR $\leq 0.81$).

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AC | dose-dense doxorubicin + cyclophosphamide |
| AC-T | doxorubicin + cyclophosphamide followed by paclitaxel |
| ADA | anti-drug antibody, also known as anti-therapeutic antibody |
| AFT | Alliance Foundation Trials |
| AJCC | American Joint Committee on Cancer |
| ALND | axillary lymph node dissection |
| ANC | absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| Atezo | atezolizumab |
| AV | atrioventricular |
| benda | bendamustine |
| BIG | Breast International Group |
| BRCA1 | breast cancer 1 gene |
| BRCA1 | breast cancer 2 gene |
| CAP | College of American Pathologists |
| CD | cluster of differentiation |
| CHEK2 | checkpoint kinase 2 |
| CHOP | cyclophosphamide, doxorubicin, vincristine, and prednisone |
| COVID-19 | Coronavirus Disease 2019 |
| CRO | contract research organization |
| CRS | cytokine-release syndrome |
| CT | computed tomography |
| CYP | cytochrome P450 |
| DCIS | ductal carcinoma in situ |
| DEHP | bis(2-ethylhexyl) phthalate |
| DFS | disease-free survival |
| DRFI | distant recurrence-free interval |
| EBC | early breast cancer |
| EC | dose-dense epirubicin + cyclophosphamide |
| ECHO | echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQ-5D-5L | EuroQoL 5-Dimension, 5-Level |

| Abbreviation | Definition |
|---|---|
| ER | estrogen receptor |
| ESMO | European Society for Medical Oncology |
| FACT-G | Functional Assessment of Cancer Therapy-General |
| FFPE | formalin-fixed paraffin embedded |
| FN | febrile neutropenia |
| G | obinutuzumab |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| GHS | global health status |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| HbcAb | hepatitis B core antibody |
| HbsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HER2 | human epidermal growth factor receptor 2 |
| HGRAC | Human Genetic Resources Administration of China |
| HIPAA | Health Insurance Portability and Accountability Act |
| HLH | hemophagocytic lymphohistiocytosis |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| IC | tumor-infiltrating immune cell |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IL | interleukin |
| ISC | Independent Statistical Center |
| iDFS | invasive disease-free survival |
| IDMC | Independent Data Monitoring Committee |
| Ig | immunoglobulin |
| IHC | immunohistochemistry |
| IJB/CTSU | Institut Jules Bordet/Clinical Trials Support Unit |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| INF | interferon |
| IRB | Institutional Review Board |
| IRR | infusion-related reaction |
| ISH | in situ hybridization |
| ITT | intention-to-treat |

| Abbreviation | Definition |
|---|---|
| IxRS | interactive voice or Web-based response system |
| LCIS | lobular carcinoma in situ |
| LHRHa | luteinizing hormone releasing hormone agonist |
| LVEF | left ventricular ejection fraction |
| MAS | macrophage activation syndrome |
| MRI | magnetic resonance imaging |
| MUGA | multiple-gated acquisition |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NGS | next-generation sequencing |
| NSCLC | non-small cell lung cancer |
| NYHA | New York Heart Association |
| OS | overall survival |
| PALB2 | partner and localizer of BRCA2 |
| PCR | polymerase chain reaction |
| PET | positron emission tomography |
| PFS | progression free survival |
| P-gp | P-glycoprotein |
| PgR | progesterone receptor |
| PIK3CA | phosphatidylinositol 3-kinase, catalytic, $\alpha$-polypeptide |
| PK | pharmacokinetic |
| PRO | patient-reported outcome |
| PTEN | phosphatase and tensin homolog |
| PVC | polyvinyl chloride |
| Q | question |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| QW | weekly |
| RFI | recurrence-free interval |
| RPBS | Research Project Biological Samples |
| RT | radiotherapy |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SC | Steering Committee |
| SFTP | Secure File Transfer Protocol |
| SLNB | sentinel lymph node biopsy |

| Abbreviation | Definition |
|---|---|
| T3 | triiodothyronine |
| T-AC/EC | paclitaxel, dose-dense doxorubicin/epirubicin, and cyclophosphamide |
| TIL | tumor-infiltrating lymphocyte |
| TNBC | triple-negative breast cancer |
| TNF | tumor necrosis factor |
| UICC | Union for International Cancer Control |
| ULN | upper limit of normal |
| WES | whole exome sequencing |
| WGS | whole genome sequencing |

# 1. BACKGROUND

## 1.1 BACKGROUND ON BREAST CANCER

Globally, breast cancer is the second most common invasive malignancy and the most common cause of cancer-related mortality in women. The majority of breast cancers in the Western world are diagnosed when the cancer is still confined to the breast, with or without locoregional lymph node spread (Sant et al. 2003; Jemal et al. 2011; Ferlay et al. 2012; Howlader et al. 2016). At these early stages (I–III, early breast cancer [EBC]), the largely asymptomatic disease is usually operable and can be treated with curative intent.

Triple-negative breast cancer (TNBC) is defined by the absence of immunostaining for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor-2 (HER2). Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBCs and their diverse gene expression patterns and underlying genomic changes, but these insights have not yet provided clear guidance for the identification of clinically effective targeted therapies currently under laboratory and clinical investigation (Ma et al. 2011). Unfortunately, TNBCs are more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype (Anders and Carey 2008). Patients with TNBCs exhibit a poor clinical outcome, generally with rapid progression and a shorter time to local and distant relapse (Dent et al. 2007).

Early-stage TNBC comprises 10%–20% of all new diagnoses of EBC defined as Stage I–III (Lehmann et al. 2011; Howlader et al. 2016). Three-year invasive disease-free survival (iDFS) rates of 81% have been reported for patients with TNBC who have received adjuvant anthracycline/taxane therapy (Sparano et al. 2015). Upon systemic relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased overall survival (OS) (Kassam et al. 2009).

## 1.2 TREATMENT FOR EARLY TRIPLE-NEGATIVE BREAST CANCER

Multi-agent chemotherapy regimens have proven benefit as neoadjuvant/adjuvant therapy for patients with early-stage TNBC, improving both disease-specific and OS outcomes (Berry et al. 2006; Senkus et al. 2015; NCCN 2016). Chemotherapy intended to reduce the risk of relapse may be given pre-operatively (neo-adjuvant setting) or post-operatively (adjuvant setting) to patients with EBC and is currently recommended for patients with TNBC in Stage I–III of the disease. Globally, chemotherapy is most often administered as adjuvant therapy; however, rates of neoadjuvant treatment use are increasing.

The most effective chemotherapy combinations used for early-stage TNBC include anthracyclines, platinum agents, cyclophosphamide, and/or taxanes (Early Breast Cancer Trialists' Collaborative Group 2005; Peto et al. 2012). Studies looking at

optimizing the dose and schedule of EBC chemotherapy regimens (Citron et al. 2003; Sparano et al. 2008; Budd et al. 2014) have established one of the optimal adjuvant regimens with respect to maximizing efficacy as doxorubicin 60 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ administered every 2 weeks (Q2W) for 4 cycles with granulocyte colony-stimulating factor (G-CSF) support, followed by weekly paclitaxel 80 mg/m$^2$ for 12 weeks; the regimen is included as a preferred option in international guidelines (Senkus et al. 2015; NCCN 2016).

However, despite having received standard anthracycline-taxane-based therapy, approximately 30%–40% of patients with clinically localized disease at diagnosis develop metastatic disease and die of the cancer (Haffty et al. 2006; Tan et al. 2008; Budd et al. 2014). Thus, there is a substantial need to improve long-term treatment outcomes for patients with early-stage TNBC.

## 1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as cluster of differentiation 80 [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T-cells.

Atezolizumab has demonstrated anti-tumor activity in both nonclinical models of cancer, as well as in patients with different tumor types. It is currently being investigated as a potential treatment across a wide variety of malignancies. Atezolizumab is approved for the treatment of urothelial carcinoma, non-small cell lung cancer, small-cell lung cancer, and triple-negative breast cancer, hepatocellular carcinoma, and melanoma. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings for different tumor types, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

### 1.3.1 Clinical Experience with Atezolizumab in Triple-Negative Breast Cancer

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions).

Much of the available safety and efficacy data in TNBC are from the five studies below:

- Study PCD4989g, a Phase Ia, multicenter, first-in-human, open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab monotherapy in patients with locally advanced or metastatic solid malignancies or hematologic malignancies
- Study GP28328, a Phase Ib multi-cohort trial of the safety and pharmacology of atezolizumab administered with bevacizumab and/or chemotherapy in patients with advanced solid tumors. Arm F of the trial is evaluating atezolizumab administered in combination with weekly nab-paclitaxel in patients with TNBC.
- Study WO29522 (IMpassion130), a randomized Phase III trial in patients with locally advanced or metastatic TNBC, previously untreated for metastatic disease. The addition of atezolizumab to nab-paclitaxel resulted in a statistically significant and clinically meaningful progression free survival (PFS) benefit and a clinically meaningful OS benefit in the PD-L1 IC positive population (PD-L1 stained tumor-infiltrating immune cells $\geq$ 1% of the tumor area by SP142 assay). The safety profile of atezolizumab + nab-paclitaxel was consistent with those of the individual treatment components and no new safety concern was identified.
- Study WO39392 (IMpassion031), a randomized Phase III trial demonstrated that neoadjuvant treatment with atezolizumab in combination with nab-paclitaxel and anthracycline-based chemotherapy provided a statistically significant and clinically meaningful improvement in the rate of pathologic complete response at definitive surgery in patients with locally advanced or early TNBC, regardless of PD-L1 expression. No significant new safety concerns were identified and the overall safety profile of atezolizumab in combination with nab-paclitaxel followed by atezolizumab in combination with doxorubicin and cyclophosphamide was consistent with the known safety profile of the individual therapeutic agents.
- Study MO39196 (IMpassion131), a Phase III study of atezolizumab and paclitaxel versus placebo and paclitaxel in patients with previously untreated locally advanced or metastatic TNBC did not show a statistically significant improvement for the primary endpoint of investigator-assessed PFS and there was also no evidence of a survival benefit in patients with PD-L1-positive metastatic TNBC when adding atezolizumab to paclitaxel. The safety profile of the atezolizumab and paclitaxel combination was consistent with the known effects of the individual study drugs.

Refer to the Atezolizumab Investigator's Brochure for details on the clinical studies involving atezolizumab as well as updated detailed safety and efficacy results.

## 1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

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

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies. Objective responses have been observed across a broad range of malignancies, including non-small cell lung cancer (NSCLC), urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. In particular, available data from the TNBC cohorts in Studies PCD4989g and GP28328 have demonstrated activity and durable responses in patients receiving atezolizumab as monotherapy or in combination with nab-paclitaxel (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

Atezolizumab in combination with taxanes (including paclitaxel and nab-paclitaxel) has also been explored. Adverse events observed were similar to those experienced with paclitaxel or nab-paclitaxel alone and have generally been manageable. The risk of overlapping toxicities between atezolizumab and paclitaxel, doxorubicin/epirubicin, and cyclophosphamide is thought to be minimal based on the mechanism of action of each product. Known serious risks associated with paclitaxel include bone marrow suppression (neutropenia, anemia, and thrombocytopenia), elevation of liver enzymes, alopecia, peripheral neuropathy, infection, and pneumonitis. Known serious risks of doxorubicin include bone marrow suppression (neutropenia, anemia, and thrombocytopenia), alopecia, nausea and vomiting, skin reactions, cardiotoxicity, and secondary acute myeloid leukemia. Known serious risks of epirubicin are bone marrow suppression (mainly leukopenia and neutropenia), infection, mucositis/stomatitis, nausea and vomiting, secondary leukemias, and cardiotoxicity. Known serious risks associated

with cyclophosphamide include bone marrow suppression (neutropenia, anemia, and thrombocytopenia), infection, renal toxicity, cystitis, cardiotoxicity, and pneumonitis. In order to mitigate any potential risks associated with this combination regimen, patients with cardiopulmonary dysfunction will be excluded from the study (see Section 4.1.2) and an Independent Data Monitoring Committee (IDMC) will regularly review unblinded safety data (see Section 3.1.1).

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

This study will enroll patients with Stage II–III TNBC (those with node-negative disease must have a tumor size $>2$ cm). The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of patients with node-negative disease. Given the relatively poor prognosis for these patients and the lack of targeted agents, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for atezolizumab in combination with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide is expected to be acceptable in this setting.

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

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-$\gamma$ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for COVID-19-related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of SARS-CoV-2 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

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

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

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.5.1).

## 2. OBJECTIVES AND ENDPOINTS

This study (Study BIG 16-05/AFT-27/WO39391, also known as ALEXANDRA/IMpassion030) will evaluate the efficacy, safety, and pharmacokinetics of adjuvant atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (referred to as atezolizumab + T-AC/EC) compared with paclitaxel followed by

dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (referred to as T-AC/EC) in patients with Stage II–III TNBC.

Specific objectives and corresponding endpoints for the study are outlined in Table 1.

**Table 1 Objectives and Corresponding Endpoints**

| Objectives | Corresponding Endpoints |
|---|---|
| **Primary Efficacy Objective:** | |
| • To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with TNBC | • iDFS, defined as the time from randomization until the date of the first occurrence of one of the following events:<br>– Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)<br>– Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)<br>– Ipsilateral second primary invasive breast cancer<br>– Contralateral invasive breast cancer<br>– Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the sites mentioned above]) that has either been histologically confirmed and/or clinically/radiographically diagnosed as recurrent invasive breast cancer<br>– Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Objectives | Corresponding Endpoints |
|---|---|
| **Secondary Efficacy Objectives:** | |
| • To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone | • iDFS in the subpopulation with PD-L1-selected tumor status (IC1/2/3)<br>• iDFS in the subpopulation with node-positive disease<br>• OS, defined as the time from randomization to death from any cause<br>• iDFS defined the same way as the primary endpoint but including second primary non-breast invasive cancer (except for non-melanoma skin cancers and in situ carcinoma of any site) as an event<br>• RFI, defined as the time from randomization until local, regional, or distant disease recurrence<br>• Distant RFI, defined as the time from randomization until distant disease recurrence only |
| • To evaluate the efficacy of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone | • DFS, defined as the time from randomization to the first occurrence of disease recurrence or death from any cause.<br>• Events defining DFS:<br>– Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)<br>– Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)<br>– Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the sites mentioned above]) that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer<br>– Contralateral invasive breast cancer<br>– Ipsilateral or contralateral DCIS<br>– Second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Objectives | Corresponding Endpoints |
|---|---|
| **Secondary Efficacy Objectives (cont.):** | |
| | – Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified it at all possible) |
| • To evaluate PROs of function and HRQoL associated with atezolizumab + T-AC/EC compared with T-AC/EC alone, as measured by the functional and HRQoL scales of the EORTC QLQ-C30 | • Mean and mean changes from baseline score in function (role, physical) and GHS/HRQoL by assessment timepoint, and between treatment arms as assessed by the functional and GHS/HRQoL scales of the EORTC QLQ-C30 |
| **Exploratory Efficacy Objectives:** | |
| • To evaluate PROs of disease/treatment-related symptoms associated with atezolizumab + T-AC/EC compared with T-AC/EC alone, as measured by the EORTC QLQ-C30 | • Mean and mean changes from baseline score in disease/treatment-related symptoms by assessment timepoint, and between treatment arms as assessed by all symptom items/scales of the EORTC QLQ-C30 |
| • To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to T-AC/EC compared with T-AC/EC alone, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical well-being subscale of the FACT-G quality-of-life instrument | • Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G |
| • To evaluate patient's health utility as measured by the EQ-5D-5L questionnaire to generate utility scores for use in economic models for reimbursement | • Utility scores of the EQ-5D-5L questionnaire |
| **Safety Objective:** | |
| • To evaluate the safety and tolerability of atezolizumab + T-AC/EC compared with T-AC/EC alone | • Occurrence and severity of adverse events as defined by NCI CTCAE (v5.0) |
| **Pharmacokinetic Objective:** | |
| • To characterize the serum pharmacokinetics of atezolizumab when administered in combination with T-AC/EC chemotherapy | • Serum concentration of atezolizumab at specified timepoints |
| **Immunogenicity Objective:** | |
| • To evaluate the immune response to atezolizumab | • Incidence of ADAs during the study relative to the prevalence of ADAs at baseline |

**Table 1 Objectives and Corresponding Endpoints (cont.)**

| Objectives | Corresponding Endpoints |
|---|---|
| **Exploratory Immunogenicity Objective:** | |
| • To evaluate potential effects of ADAs | • Relationship between ADA status and efficacy, safety, or PK endpoints |
| **Exploratory Biomarker Objective:** | |
| • To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in tumor tissue and blood and their association with efficacy endpoints including, but not limited to, disease recurrence | • Relationship between tumor derived RNA-based immune and tumor gene signatures and efficacy endpoints including, but not limited to, the primary endpoint (iDFS)<br>• Relationship between tumor-based TILs and/or CD8 IHC and efficacy endpoints including, but not limited to, the primary endpoint (iDFS) |
| • To identify biomarkers that are associated with resistance to atezolizumab in combination with T-AC/EC or can increase the knowledge and understanding of disease biology | • Relationship between biomarkers in blood and tumor tissue between pretreatment and post-recurrence samples collected at disease recurrence. These biomarkers may include, and are not limited to, the following:<br>– Acquired mutations assessed using DNA°NGS<br>– Changes in the tumor immune microenvironment and biology as assessed by RNA profiling and IHC |

ADA = anti-drug antibodies; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQoL 5 Dimension, 5 Level; FACT-G = Functional Assessment of Cancer Therapy-General; GHS = global health status; HRQoL = health-related quality of life; IC = tumor-infiltrating immune cell, iDFS = invasive disease-free survival; IHC = immunohistochemistry; NCI CTCAE (v5.0) = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; NGS = next-generation sequencing; OS = overall survival; PK = pharmacokinetic; PRO = patient-reported outcomes; QLQ-C30 = Quality of Life Questionnaire-Core 30; RFI = recurrence-free interval; T-AC/EC = paclitaxel, dose-dense doxorubicin/epirubicin, and cyclophosphamide; TILs = tumor-infiltrating lymphocyte; TNBC = triple-negative breast cancer.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

This is a global Phase III, open-label, randomized, controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of adjuvant treatment with atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with newly diagnosed TNBC who have completed surgery with curative intent of their primary tumor and are candidates for adjuvant systemic therapy following surgery.

The HER2 and ER/PgR status will be used to define TNBC. The HER2 negativity will be defined by central laboratory assessment using in situ hybridization (ISH) or immunohistochemistry (IHC) assays per the criteria outlined in the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines for HER2 testing (Wolff et al. 2018). ER/PgR negativity will be defined by central laboratory

assessment using IHC assays per the criteria outlined in the ASCO/CAP guidelines for ER/PgR testing (Allison et al. 2020). Central laboratory assessment will occur prior to randomization. Patients whose tumors are not confirmed to be triple negative by central laboratory assessment will not be eligible. The PD-L1 status will be assessed by central laboratory. Patients whose tumor tissue is not evaluable for PD-L1 will not be eligible. All site and study team staff will be blinded to PD-L1 status. For information regarding particular situations when unblinding to PD-L1 status to the investigator may be allowed see Section 4.3.

Patients who provide informed consent and are eligible will be randomized in a 1:1 ratio to receive either of the following treatment regimens:

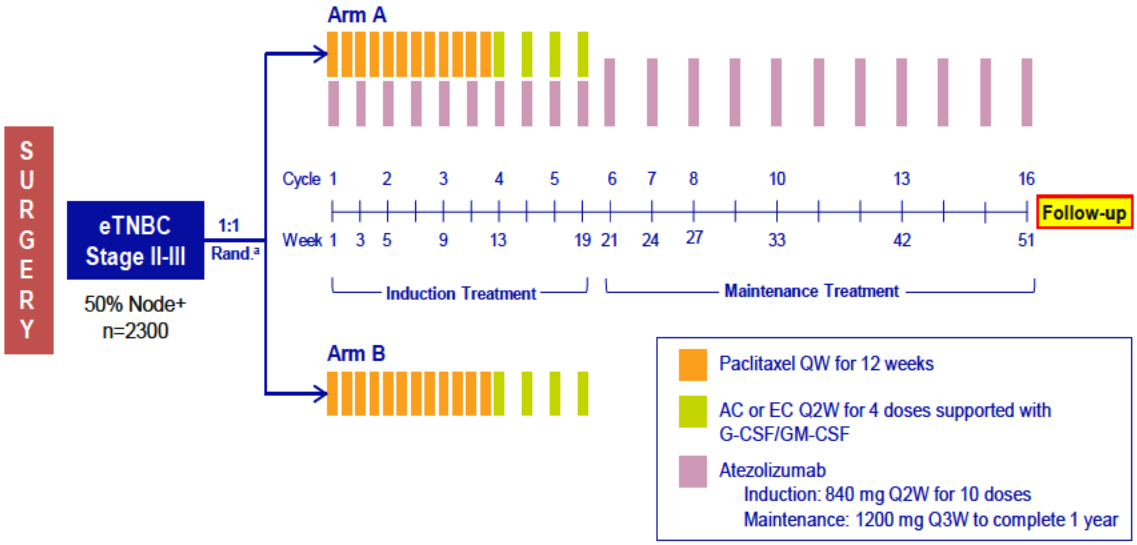
- **Arm A**: Atezolizumab and Chemotherapy
  - Atezolizumab: atezolizumab (840 mg) administered via IV Q2W in combination with chemotherapy (as described below), followed by atezolizumab maintenance therapy (1200 mg IV infusion every 3 weeks [Q3W]) to complete a total duration of 1 year of atezolizumab treatment from the first administration of atezolizumab.
  - Chemotherapy: paclitaxel (80 mg/m$^2$) administered via IV infusion weekly (QW) for 12 weeks followed by dose-dense doxorubicin (60 mg/m$^2$) or dose-dense epirubicin (90 mg/m$^2$) IV (investigator's choice)+cyclophosphamide (600 mg/m$^2$) IV repeated Q2W for 4 doses.
  - Granulocyte colony stimulating factor (e.g., filgrastim or pegfilgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF) treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin+cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, European Organisation for Research and Treatment of Cancer (EORTC), or European Society for Medical Oncology (ESMO) guidelines or per local standard practice (see Section 4.5.1).
- **Arm B**: Chemotherapy alone
  - Paclitaxel (80 mg/m$^2$) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m$^2$) or dose-dense epirubicin (90 mg/m$^2$) IV (investigator's choice)+cyclophosphamide (600 mg/m$^2$) IV repeated Q2W for 4 doses.
  - Granulocyte colony-stimulating factor (e.g., filgrastim or pegfilgrastim) or GM-CSF treatment is permitted for patients receiving chemotherapy and is required during the dose-dense doxorubicin/epirubicin+cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, EORTC, or ESMO guidelines or per local standard practice (see Section 4.5.1).

The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of patients with node-negative disease.

Patients who do not initially meet all eligibility criteria, other than TNBC status, may be re-screened once.

The study schema is presented in Figure 1.

**Figure 1 Study Schema**




AC = dose-dense doxorubicin + cyclophosphamide;
EC = dose-dense epirubicin + cyclophosphamide; eTNBC = early triple-negative breast cancer; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; QW = weekly; Q2W = every 2 weeks; Q3W = every 3 weeks; Rand = randomization.

Notes: The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of node-negative patients.
Node-negative patients with tumors ≤2 cm in size are not eligible to participate in this study.
G-CSF/pegylated G-CSF/GM-CSF will be used with each dose of AC/EC.
In the induction period, 1 cycle = 4 weeks; in the maintenance period, 1 cycle = 3 weeks.

[a] Randomization should occur no more than 8 weeks after definite surgery, and study drug administration should begin within 1 week after randomization but no sooner than 2 weeks after surgery.

Randomization will be stratified by the following factors:

- Axillary nodal status (0 vs. 1–3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs. mastectomy)
- Tumor PD-L1 status (tumor-infiltrating immune cell [IC] 0 vs. IC1/2/3)

Randomization should occur no more than 8 weeks (56 days) after definitive surgery, and study drug administration should begin within 1 week (7 days) after randomization but no sooner than 2 weeks (14 days) after last surgery. In case of multiple surgeries performed for the breast cancer treatment, this time period should count starting from the last performed curative surgery.

To ensure comparability of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will undergo similar assessments as patients in Arm A. These assessments will consist of formal clinic visits for evaluation of symptoms and adverse events, including cardiac toxicity. Following the induction period, patients in Arm B will continue patient-reported outcome (PRO) assessments, laboratory evaluations, left ventricular ejection fraction (LVEF) monitoring, and limited physical examinations on a regular basis for the first year after randomization. For patients in both arms, PRO assessments, LVEF monitoring, physical examinations and other assessments will continue at a reduced frequency after the first year after randomization.

Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

In case of unacceptable toxicity attributed to chemotherapy in Arm A, atezolizumab should be stopped and restarted together with chemotherapy if there is no contraindication. In cases where chemotherapy is permanently discontinued, atezolizumab may be restarted if there is no contraindication and should be based on on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed. In case of toxicities attributed to atezolizumab, chemotherapy may be continued independently of atezolizumab if there is no contraindication. Atezolizumab may be restarted when the conditions for retreatment have been met. When atezolizumab is restarted, the infusions should remain synchronized and aligned with the chemotherapy schedule and it should be administered at a scheduled atezolizumab visit (i.e., missed doses of atezolizumab will not be made up).

Dose delay and modification guidelines for chemotherapy are provided in Section 5.1.6. Management guidelines for toxicities associated with atezolizumab are provided in Appendix 9.

Treatment will be discontinued in the event of disease recurrence, unacceptable toxicity/adverse event occurrence, pregnancy, withdrawal of consent, significant protocol violations, or study termination. Patients who prematurely discontinue from the study will not be replaced. Except for patients who withdraw consent from study follow-up, those who have prematurely discontinued from treatment will be followed for safety (including cardiac toxicity) and efficacy endpoints.

Efficacy, safety, laboratory, PROs, pharmacokinetic (PK) measures, and biomarkers will be assessed throughout the study. Following completion of study treatment, all patients will continue to be followed for efficacy, safety, and PRO objectives until the end of the study.

Safety assessments will include the occurrence and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE [v5.0]). The LVEF will be assessed serially by echocardiogram (ECHO)/multiple-gated acquisition (MUGA) scans. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including tumor tissues, as well as plasma and blood, will be collected for exploratory biomarker assessments.

### 3.1.1 Independent Data Monitoring Committee

An IDMC will evaluate safety and efficacy data during the study. No IDMC member may participate in the Study as an investigator, co-investigator, sub-investigator, committee member (other than IDMC), or patient, or in any other capacity that might compromise his or her independence and privileged activities within the IDMC. In order to ensure independence, members should have no involvement in the design and conduct of the Study except through their role on the IDMC and have no financial or other interests in the sponsor's business or other Study organizers (BIG, AFT, FS, and IJB) that could influence (or be perceived to influence) their objectivity in evaluating the study. The IDMC will follow a charter that outlines the IDMC roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis. The first safety review will occur when 50 patients in each treatment arm have received at least 2 doses of doxorubicin/epirubicin and cyclophosphamide (with or without atezolizumab, respectively) and the relevant data has been entered in the electronic Case Report Form (eCRF). Subsequent safety reviews will occur at least once every 6 months during the study until the last patient has completed or discontinued study treatment.

*A formal futility analysis will be conducted in mid-March 2023 to determine the ability of the study to provide an acceptable benefit-risk assessment upon trial completion. This will include an efficacy interim analysis of iDFS of available efficacy (approximately 62% of the total iDFS events) and safety data.*

*Additional*, unblinded efficacy data will be reviewed as part of an interim analysis, scheduled to occur after approximately 80% (approximately *312 events*) of the targeted iDFS events are observed in the intent-to-treat (ITT) population (see Section 6.9.1). All summaries and analyses for the IDMC review will be prepared by an Independent Statistical Center (ISC).

After reviewing the data, the IDMC will make a recommendation to the Interface Committee as described in the Interface Committee Charter and the IDMC Charter. Final decisions will rest with the Steering Committee (SC). Rules for the decisions if consensus is not achieved are described in the Interface Committee and Executive Committee Charters.

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

## 3.2 END OF STUDY AND LENGTH OF STUDY

To enable long-term follow-up for survival and safety information, the study is planned to end when approximately $299\ deaths$ have been observed for the analysis of OS.

The total length of this study will be from randomization of the first patient to last patient, last visit for the final analysis of OS, which is estimated to occur approximately 7 years after the first patient is randomized.

The study may be terminated, including long-term follow-up, at any time (e.g., if emerging safety signals indicate a potential health hazard to patients).

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered as a flat dose of 840 mg Q2W during the chemotherapy portion of treatment to align with the chemotherapy schedule (Cycles 1–5). For the remainder of atezolizumab treatment (Cycles 6–16), atezolizumab will be administered at a flat dose of 1200 mg Q3W for patient convenience. The total duration of atezolizumab treatment will be one year from first administration of atezolizumab.

The fixed dose of 840 mg Q2W was selected with the intent of selecting a dose that is the exposure equivalent of the fixed dose of 1200 mg Q3W (weight-based equivalent of 15 mg/kg), which has been approved for treating patients with urothelial carcinoma and NSCLC (TECENTRIQ™ Package Insert). Of note, the exact equivalent dose is 800 mg; however, because atezolizumab is formulated at a concentration of 60 mg/mL, 800 mg corresponds to a volume of 13.33 mL, and in the interest of simplifying administration, the exact dose used in this study will be 840 mg, corresponding to a volume of 14 mL, which can be accurately administered with a single syringe. The 840-mg dose is not expected to result in meaningfully different exposure compared with an 800-mg dose.

Anti-tumor activity has been observed across doses ranging from 1–20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both

nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

### 3.3.2 Rationale for Patient Population and Analysis Groups

This study will enroll patients with Stage II–III operable TNBC, regardless of PD-L1 expression (Sections 4.1.1 and 4.1.2). Those with node-negative disease must have a tumor size >2 cm. The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of patients with node-negative disease.

TNBC will be defined by prospective central laboratory assessment using ISH or IHC assays for HER2 assessment and IHC assays for ER/PgR assessment per ASCO/CAP guidelines (Allison et al. 2020; Wolff et al. 2018).

Patients with Stage II–III TNBC were selected for this study because increased tumor size and lymphovascular involvement have been identified as poor prognostic variables and have been associated with decreased disease-free survival (DFS) and increased likelihood of early metastatic disease in patients with TNBC (Pistelli et al. 2013; Rosa Mendoza et al. 2013). Not-yet-published internal analyses from the California Cancer Registry found survival rates in patients with Stage II–III disease to be significantly lower than those of patients diagnosed with Stage I disease (3-year OS rate of 94.2% [95% CI: 93.3% to 95.0%] for Stage I; 86.2% [95% CI: 85.1% to 87.2%] for Stage II; 58.8% [95% CI: 56.3% to 61.2%] for Stage III, and 16.4% [95% CI: 13.2% to 19.8%] for Stage IV; data on file). By selecting a patient population that has an increased rate of disease recurrence (larger tumor size) and poorer clinical outcomes, and by further enriching this with patients with node-positive disease, the study will enroll patients with TNBC who have the highest unmet medical need.

In Study PCD4989g, atezolizumab monotherapy was generally well tolerated and activity was demonstrated in patients with advanced malignancies, including TNBC (refer to the Atezolizumab Investigator's Brochure; Emens et al. 2015). Efficacy analyses were performed on the 93 patients with TNBC who were dosed by 15 May 2015. These 93 patients had been preselected for a PD-L1 status of IC0/1 (n=34) or 2/3 (n=56). Three patients had unknown PD-L1 status. The majority of patients had received at least 4 prior systemic therapies (89%). Confirmed responses were seen in 9.7% of patients (95% CI: 4.5% to 17.6%), with a majority of responses included in the IC2/3 population (objective response rate 12.5% for IC2/3, and 5.9% for IC0/1).

In Study GP28328, the combination of atezolizumab and nab-paclitaxel was studied in 32 patients with TNBC (Adams et al. 2016). Of the efficacy-evaluable patients, 13 patients received the treatment combination as first-line therapy, 9 patients received the combination as second-line therapy, and 10 patients received it in the third-line or later setting. Confirmed responses were seen in 38% of patients (95% CI: 21% to 56%), with responses reported in patients regardless of PD-L1 expression. Results from

Study GP28328 support the hypothesis that tumor cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens. Boosting tumor-specific T-cell immunity in this setting by blocking the PD-L1 pathway may result in deeper and more durable responses than those observed with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression. The inclusion of patients with all levels of PD-L1 expression in this study will enable a robust assessment of this hypothesis.

### 3.3.3 Rationale for Comparator of Paclitaxel Followed by Anthracycline and Cyclophosphamide

In the adjuvant setting, anthracycline/taxane chemotherapy-based regimens have routinely been used for TNBC resulting in reported 5-year DFS rates of 76%–82% (Henderson et al. 2003; Mamounas et al. 2005; Sparano et al. 2015) leaving room for improvement in outcomes. One of the most commonly used regimens is dose-dense doxorubicin + cyclophosphamide followed by paclitaxel (AC-T), consisting of doxorubicin 60 mg/m$^2$ plus cyclophosphamide 600 mg/m$^2$ Q2W for four cycles (i.e., 4 doses each), followed by paclitaxel administered at either 175 mg/m$^2$ Q2W for four cycles (Citron et al. 2003) or 80 mg/m$^2$ QW for 12 weeks (Budd et al. 2014); this regimen is included as a preferred option in international guidelines (Senkus et al. 2015; NCCN 2016). Dose-dense epirubicin 90 mg/m$^2$ plus cyclophosphamide 600 mg/m$^2$ Q2W for 4 cycles (i.e., 4 doses each) followed by a taxane has also been studied with similar outcomes (Del Mastro et al. 2015; Foukakis et al. 2016).

Adjuvant paclitaxel will be administered prior to doxorubicin/epirubicin + cyclophosphamide chemotherapy in this study. This sequence of chemotherapy agents was selected in order to maximize the potential for a robust initial immune response because there is less reported neutropenia and potentially lower usage of steroids as a prophylactic anti-emetic regimen with paclitaxel compared with doxorubicin/epirubicin + cyclophosphamide. Several small Phase II prospective studies and one retrospective study have evaluated the impact of changing the sequence of administration for anthracyclines and taxanes in the adjuvant setting for TNBC (Cardoso et al. 2001; Piedbois et al. 2007; Puhalla et al. 2008; Wildiers et al. 2009; Alvarez et al. 2010; Abe et al. 2013). In studies where efficacy results were reported, reversing the sequence of adjuvant breast cancer chemotherapy by starting with the taxane and following with an anthracycline-containing regimen did not impact recurrence rates (Bines et al. 2014).

The safety of atezolizumab in combination with anthracyclines is being explored in BO29563, a Phase Ib/II study evaluating atezolizumab (Atezo) in combination with either obinutuzumab (G) + bendamustine (benda) or obinutuzumab (G) + cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in patients with follicular lymphoma or rituximab + CHOP in patients with diffuse large B-cell lymphoma. During the

safety run-in phase, patients received 6 cycles of induction treatment with either Atezo-G-benda or Atezo-G-CHOP. As of 19 July 2016, preliminary data from 7 patients who completed at least 3 cycles of induction treatment indicated that the combination of Atezo-G-CHOP was well tolerated. None of the stopping criteria defined for the safety run-in phase of the study were met. There were no treatment-related Grade 3 and 4 adverse events during Cycles 2 and 3 (i.e., safety observation window). No treatment delays or treatment discontinuations due to adverse events were observed.

### 3.3.4 Rationale for Invasive Disease-Free Survival as Primary Endpoint

The primary objective of Study BIG 16-05/AFT-27/WO39391 is to evaluate the efficacy of adjuvant treatment with atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with newly diagnosed TNBC as measured by iDFS.

An expert panel was convened to develop standardized definitions for efficacy endpoints in adjuvant breast cancer trials; this panel proposed the adoption of a broad composite endpoint that excludes all in situ cancer events (Hudis et al. 2007). The presence of in situ disease alone will, therefore, not be considered an event for iDFS in this study.

It is important to note; however, that non-fatal second non-breast primary cancers will not be included as events for the primary endpoint because they generally do not relate to breast cancer-specific efficacy. This differs from the panel's proposed definition (Hudis et al. 2007). Several recent breast cancer registrational studies investigating adjuvant aromatase inhibitors and adjuvant anti-HER2 treatments have also excluded these as events (see Hudis et al. 2007 and references therein; Hoffmann-La Roche 2011, 2013).

### 3.3.5 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. Randomization will be stratified by PD-L1 expression as assessed by IHC. In addition to the assessment of PD-L1 status, other exploratory biomarkers potentially related to clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Presence of tumor-infiltrating lymphocytes (TILs) and cytotoxic T-cell biology (effector T-cells) are associated with good prognosis in adjuvant and neoadjuvant chemotherapy treated patients with TNBC (Denkert et al. 2010). Evaluation of TILs and CD8 T-cells may be analyzed in tumor tissue, by hematoxylin and

eosin stain, IHC, and/or RNA-based gene expression signatures reflecting these biologies.

Triple-negative breast cancer is a genomically heterogeneous disease. Tumor genomic somatic alterations, such as tumor mutation load and PTEN loss (phosphatase and tensin homolog), have been associated with response or resistance to checkpoint inhibitors, while mutations in genes leading defective antigen presentation or enhanced activation of the PIK3CA (phosphatidylinositol 3-kinase, catalytic, $\alpha$-polypeptide) pathway have been described to reduce PD-L1/PD-1 activity (Schalper et al. 2014; Lee et al. 2015).

Patients are required to undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of clinical or radiographic disease recurrence to evaluate tumor tissue biomarkers related to mechanisms of acquired resistance and disease recurrence. Examples of when tumor biopsy sample collection may be considered not clinically feasible include, but are not limited to, cases where the location of the tumor renders tumor biopsy unsafe or not clinically feasible per the investigator due to patient concerns or is prohibited by the institution or country.

Blood samples will be collected at baseline and during the study to evaluate changes in biomarkers. Changes in biomarkers, such as cytokines associated with T-cell activation, circulating tumor DNA concentration, and T-cell subpopulations, may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints may be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

Tumor and blood samples collected at baseline and, if deemed clinically feasible by the investigator, tumor tissue collected at the time of disease recurrence may enable DNA and RNA sequencing, as well as protein or metabolite analysis, to identify biomarkers that may be predictive and/or prognostic of recurrence to a more severe disease state, associated with acquired resistance to study treatment, or increase the knowledge and understanding of disease biology.

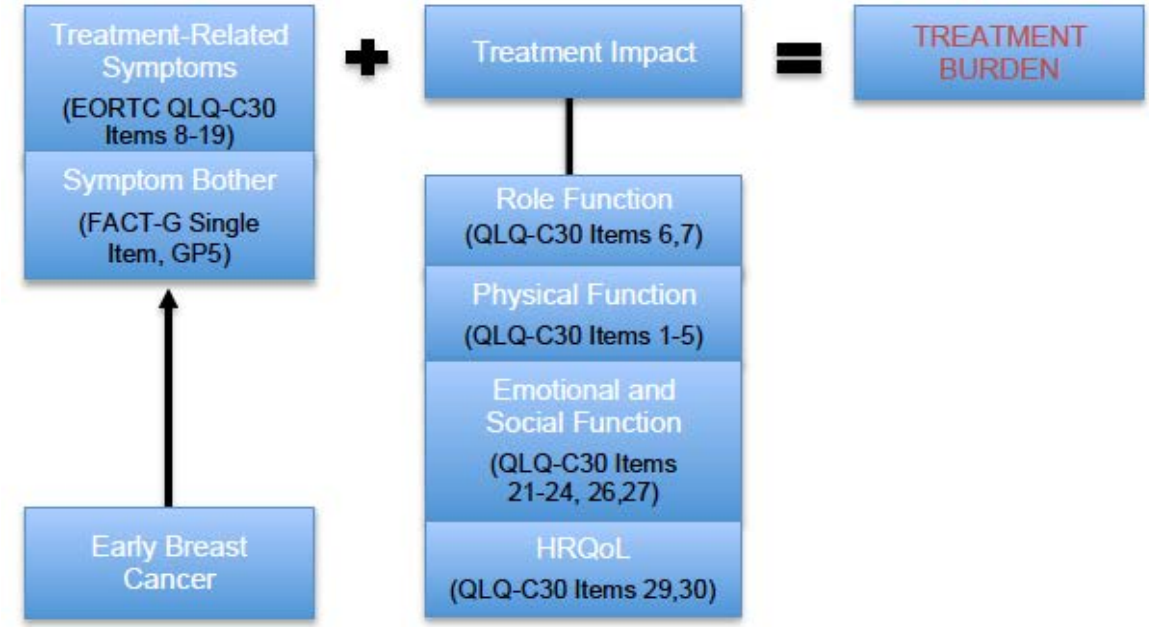
Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole genome sequencing (WGS) provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies, after endorsement by the SC. 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 Patient-Reported Outcome Assessments

EBC is largely asymptomatic, with the majority of newly diagnosed patients exhibiting no disease-specific, discernable symptoms (Barret et al. 2009; Ryerson et al. 2015). Therefore, toxicities, the corresponding treatment-related symptoms, and their impact define the patient experience (i.e., how patients feel and function). These are important aspects to consider to help inform on the overall clinical benefit of a novel drug for this potentially curable indication. Treatment-related symptoms associated with EBC regimens can have significant impact on patients' lives, including their ability to conduct activities of daily living; on physical functioning; and on emotional and social aspects (Petersen et al. 2016). It is therefore critical to document the burden associated with EBC treatment and understand the experience of treatment-related symptoms and their impact directly from patients to further inform benefit-risk assessment and treatment decision-making (Montazeri 2008; Au et al. 2010; FDA 2013; FDA 2015; EMA 2016).

A comprehensive assessment of treatment burden from the patient's perspective in this study will be conducted and will include a global assessment of the impact of treatment on patients' functioning (role, physical) and health-related quality of life (HRQoL) as secondary endpoints, as well as the experience of treatment-related symptoms and their associated level of bother and the impact on emotional and social functioning as exploratory endpoints. The global health status (GHS)/HRQoL, functional, and disease/treatment-related symptom items and scales of the EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30; see Appendix 3), and the treatment bother item GP5 from the Functional Assessment of Cancer Therapy-General (FACT-G; see Appendix 4) quality-of-life instrument will all be used to assess patients' treatment burden (see Figure 2).

**Figure 2 Documenting Treatment Burden in Early Breast Cancer Patients**




EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; HRQoL = Health-related quality of life; QLQ-C30 = Quality of Life Questionnaire Core 30.

Given the duration of treatment and the potential for long-term treatment impact, all PRO measures will be assessed at specified timepoints while patients are on treatment and after treatment discontinuation as defined in the schedule of activities (see Appendix 1). All PRO data collected will be analyzed per published scoring manuals (Cella 1997; Fayers et al. 2001) to support and inform the benefit-risk assessment of atezolizumab therapy.

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

Approximately 2300 patients with newly diagnosed Stage II–III primary invasive breast cancer that is of triple negative phenotype (as determined by the central pathology laboratory), and who will be treated with adjuvant systemic chemotherapy following definitive surgery, will be enrolled in this study. It is estimated that the study will enroll patients over approximately 4 years.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability to comply with protocol, in the investigator's judgment
- Women or men aged ≥ 18 years at time of signing ICF
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

- Non-metastatic operable Stage II–III breast cancer
  - Patients with node-negative disease must have a pathological tumor size >2 cm. Patients with node-negative multifocal, multicentric or bilateral breast cancer are eligible providing that at least one lesion is >2 cm in size.
- Histologically documented TNBC (negative HER2, ER, and PgR status)
  - HER2 negativity will be defined by central laboratory assessment using ISH or IHC assays per ASCO/CAP criteria (Wolff et al. 2018) and ER/PgR negativity will be defined by central laboratory assessment using IHC per ASCO/CAP criteria (Allison et al. 2020). Central laboratory assessment will occur prior to randomization.
  - Patients with multifocal invasive tumors (more than one tumor confined to the same quadrant as the primary tumor) or multi-centric invasive tumors (more than one tumor in different quadrants of the same breast) are eligible provided all discrete lesions are sampled and centrally confirmed as TNBC. Patients with non-TNBC invasive components are not eligible to participate in this study.
- Confirmed tumor PD-L1 evaluation as documented through central testing of a representative tumor tissue specimen.
- Adequately excised: Patients must have undergone either breast-conserving surgery or mastectomy/nipple- or skin-sparing mastectomy.
  - For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. In cases in which the patient underwent breast-conserving surgery and there was a microscopic positive deep margin (with no other positive margins), if the tumor was resected up to the chest wall muscle and the surgeon considers that a mastectomy will not provide a negative deep margin, the patient does not need to undergo a mastectomy in order to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.
  - For patients who undergo mastectomy/nipple- or skin-sparing mastectomy, margins must be free of gross residual tumor. It is recommended that patients should have a negative microscopic margin in accordance with local pathology protocol. Patients with a microscopic positive deep margin are eligible (see radiotherapy [RT] guidelines in Appendix 8).
- Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 8th edition): Patient must have had sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND) for evaluation of pathologic nodal status.

- Axillary nodal dissection(s) should yield a total of at least six nodes (including the axillary lymph nodes resected at the SLNB plus the lymph nodes collected at the axillary nodal dissection).
- Patients with positive SLNB should undergo axillary dissection unless all of the following characteristics apply (Giuliano et al. 2011):

  No palpable nodes

  No more than 2 pathologically positive lymph nodes

  Breast-conserving surgery has been completed with tangential whole breast irradiation planned OR mastectomy with regional nodal radiotherapy planned.

  Clinical tumor size $\leq$ T2 (5 cm)
- In the case that all of the above are applicable, it is not mandatory to have the axillary dissection but it is left at the discretion of the investigator as per site standard practice.
- In the case of subjects with tumors $>$ 2cm and regional lymph node found to have micrometastases or isolated tumor cells. Pathological classification of regional lymph node micrometastases (tumor deposits $>$ 0.2 mm and $\leq$ 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0.
- The study population will be enriched for patients with node-positive disease such that the final population will contain at least 50% node-positive patients.

- Patients with synchronous bilateral invasive disease are eligible only if all bilateral invasive lesions are histologically confirmed as triple negative by central laboratory and have completed adequate pathological tumor-node metastasis staging bilaterally as described above.
- No more than 8 weeks (56 days) may elapse between definitive breast surgery (or the last surgery with curative intent if additional resection is required for breast cancer) and randomization.
- Baseline LVEF $\geq$ 53% measured by ECHO (preferred) or MUGA scans
  - Baseline LVEF to be conducted within 28 days prior to randomization.
- Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 28 days prior to randomization:
  - Absolute neutrophil count (ANC) $\geq$ 1500 cells/$\mu$L (without G-CSF support within 2 weeks prior to Cycle 1, Day 1)
  - Lymphocyte count $\geq$ 500 cells/$\mu$L
  - Platelet count $\geq$ 100,000 cells/$\mu$L (without transfusion within 2 weeks prior to Cycle 1, Day 1)
  - Hemoglobin $\geq$ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - AST, ALT, and alkaline phosphatase $\leq$ 2.5 $\times$ the upper limit of normal (ULN)

  - Serum total bilirubin $\leq 1.0 \times$ ULN

    Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN within 28 days prior to randomization
  - For patients receiving therapeutic anticoagulation: stable anticoagulant regimen and stable INR during the 28 days immediately preceding randomization
  - Creatinine clearance $\geq 30$ mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin $\geq 2.5$ g/dL
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HbsAg) test at screening
- Negative total hepatitis B core antibody (HbcAb) test at screening, or positive total HbcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening
  - The HBV DNA test will be performed only for patients who have a positive total HbcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
  - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Representative formalin-fixed, paraffin embedded (FFPE) tumor specimen from surgical resection in paraffin blocks (preferred) or approximately 25 unstained slides (minimum of 20 slides), with an associated pathology report documenting locally assessed ER, PgR, and HER2 negativity.
  - Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated centrally for PD-L1 expression prior to enrollment. Fine-needle aspiration, brushing, cell pellet from cytology specimens are not acceptable. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible.
  - If multiple tumor specimens are submitted, 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.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the

last dose of atezolizumab, or 6 months after the last dose of paclitaxel or doxorubicin/epirubicin, or 12 months after the last dose of cyclophosphamide, whichever is later. Women must refrain from donating eggs during the same period.

  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and 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, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate 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 $<$1% per year during the treatment period and for 6 months after the last dose of paclitaxel, or doxorubicin/epirubicin or 12 months after the last dose of cyclophosphamide, whichever is later. Men must refrain from donating sperm during this same period.
  - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of paclitaxel, or doxorubicin/epirubicin or 12 months after the last dose of cyclophosphamide, whichever is later, to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
- Women who are not postmenopausal ($\geq$12 months of non-therapy-induced amenorrhea) and have not undergone a sterilization procedure must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires

### 4.1.2 Exclusion Criteria

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

- Prior history of invasive breast cancer

- Any T4 tumor as defined by tumor-node metastasis classification in UICC/AJCC, 8th edition, including inflammatory breast cancer
- For the currently diagnosed breast cancer, any previous systemic anti-cancer treatment (e.g., neoadjuvant or adjuvant), including, but not limited to, chemotherapy, anti-HER2 therapy (e.g., trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib, or other tyrosine kinase inhibitors), hormonal therapy, or anti-cancer RT other than planned in the context of this study and described in Appendix 8.
- Previous therapy with anthracyclines or taxanes for any malignancy
- History of DCIS and/or LCIS that was treated with any form of systemic, hormonal therapy, or RT to the ipsilateral breast where invasive cancer subsequently developed
  - Patients who had their DCIS/LCIS treated only with surgery and/or contralateral DCIS treated with RT are allowed to enter the study.
- Contraindication to RT when adjuvant RT is clinically indicated
- Cardiopulmonary and/or cerebrovascular dysfunction as defined by any of the following prior to randomization:
  - History of NCI CTCAE (v5.0) Grade $\geq$ 2 symptomatic congestive heart failure or New York Heart Association (NYHA) Class $\geq$ II
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 Mobitz 2, or third-degree AV-block])
  - Significant symptoms (Grade $\geq$ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to randomization
  - Uncontrolled hypertension (systolic blood pressure $>$ 160 and/or diastolic blood pressure $>$ 100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
  - Cerebrovascular ischemic event (e.g., ischemic within 12 months prior to randomization)
- Prior malignancies within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (i.e., adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the paclitaxel (e.g., polyoxyl 35 castor oil), cyclophosphamide, or doxorubicin/epirubicin formulations
- Known allergy or hypersensitivity to G-CSF or GM-CSF formulations
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 6 for a more comprehensive list of autoimmune diseases and immune deficiencies) with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.
  - Patients with controlled Type I diabetes mellitus who are on an insulin regimen may be eligible for this study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all the following conditions are met:

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

    Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

    There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Current treatment with anti-viral therapy for HBV
- Urinary outflow obstruction
- Active tuberculosis
- Severe infections within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during study treatment
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study or within 5 months after the last dose of atezolizumab
  - Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to initiation of study treatment, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists or immune checkpoint-blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] alpha agents) within 2 weeks prior to initiation of study treatment or anticipation of need for systemic immunosuppressive medication during the study
  - 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 based on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.
- Pregnant or lactating, or intending to become pregnant during the study
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease
- Under any legal protection (tutorship/curatorship).

## 4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label, controlled study.

After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established, the study site will enter demographic and baseline characteristics in the interactive voice or Web-based response system (IxRS). For those patients who are eligible for enrollment, the study site will obtain the patient's identification number and treatment assignment from the IxRS. Patients should receive their first dose of study treatment the day of randomization, if possible, but no later than 7 days after randomization, unless within 2 weeks after surgery. Patients should not receive their first dose of study treatment within 2 weeks after surgery. In this case, patients may receive their first dose of study treatment outside the window.

Randomization will occur in a 1:1 ratio using a permuted-block randomization method. Patients will be randomized to one of two treatment arms: atezolizumab + T-AC/EC or T-AC/EC. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the following stratification factor categories at baseline. Randomization will be stratified by the following factors:

- Axillary nodal status (0 vs. 1–3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs. mastectomy)
- Tumor PD-L1 status (IC0 vs. IC1/2/3)

## 4.3 PD-L1 UNBLINDING

All sites and study team staff will be blinded to PD-L1 status. The PD-L1 results may be provided for an individual patient, after discussion with and approval by IJB, only if all the following criteria are met:

- Patient has experienced an incurable local-regional invasive breast cancer recurrence or distant recurrence
- Investigator provides rationale for the request indicating the result is required for a current treatment decision
- It is not possible to obtain a PD-L1 result otherwise due to lack of available testing at the site OR in the following scenario:
  - Samples adequate for testing PD-L1 are not available to be returned to the site by Central Laboratory within a week

    AND
  - The investigator confirms the following:

    No other tumor samples for the subject are available at the site

    AND

No attainable sample for assessment of PD-L1 status from metastatic disease (for example, a biopsy is not feasible due to location of metastases, patient refusal, etc.)

Only the investigator will be provided the PD-L1 status results. The study team will remain blinded to a subject's PD-L1 status.

Patients that have screen failed can request their PD-L1 status without the requirements mentioned above.

## 4.4 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

### 4.4.1 Study Treatment Formulation, Packaging, and Handling

#### 4.4.1.1 Atezolizumab

The atezolizumab 1200 mg drug product will be supplied by the Sponsor in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

The atezolizumab 840 mg drug product will be supplied by the Sponsor in a single-use, 15-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 14 mL (840 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 14 mL volume. The formulation of atezolizumab 840-mg drug product is identical to that of atezolizumab 1200-mg drug product.

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

#### 4.4.1.2 Background Treatment

For information on the formulation, packaging, and handling of paclitaxel, doxorubicin/epirubicin, cyclophosphamide, and G-CSF/GM-CSF, see the local prescribing information for the respective treatments.

### 4.4.2 Study Treatment Dosage, Administration, and Compliance

Any dose modification should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 9.

#### 4.4.2.1 Atezolizumab (Arm A Only)

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg Q2W (14 [±3] days) in combination with T-AC/EC chemotherapy. Upon completion of chemotherapy, atezolizumab will be continued as maintenance therapy at a dose of 1200 mg administered by IV infusion Q3W (21 [±3] days) to complete 1 year of treatment (i.e., approximately 1 year total duration of atezolizumab therapy from first administration of atezolizumab).

In the induction (chemotherapy) period, 1 cycle = 4 weeks; in the maintenance period, 1 cycle = 3 weeks.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

**Table 2 Administration of First and Subsequent Atezolizumab Infusions**

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

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 9.

No dose modification for atezolizumab is allowed. If atezolizumab is held due to adverse events, missed doses will not be made up.

If chemotherapy is permanently discontinued because of toxicity, atezolizumab may be continued as scheduled if there is no contraindication and should be based on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed.

Treatment (including atezolizumab and chemotherapy, if applicable) will be discontinued in the event of disease recurrence while patient is receiving therapy.

#### 4.4.2.2 Background Treatment

Patients will receive paclitaxel (80 mg/m2) administered via IV infusion QW for 12 weeks followed by dose-dense doxorubicin (60 mg/m2) or dose-dense epirubicin (90 mg/m2) IV (investigator's choice)+cyclophosphamide (600 mg/m2) administered via IV infusion Q2W with G-CSF/GM-CSF support for 4 cycles (i.e., a total of 4 doses of doxorubicin/epirubicin and cyclophosphamide).

Note: For chemotherapy dosing, body surface area should be calculated according to patient actual weight and not corrected for ideal weight, nor capped for a maximum body surface area of 2 m2. No capping should be implemented.

Dose delays and dose reductions for toxicity are permitted. In case of dose reduction of chemotherapy due to an adverse event, it is not possible to re-increase the dose of chemotherapy, even after complete resolution of the adverse event.

Guidelines for dosage modification and treatment interruption or discontinuation due to the development of an adverse event are provided in Section 5.1.6

If chemotherapy is permanently discontinued as a result of toxicity, atezolizumab may be continued as scheduled if there is no contraindication and should be based on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed.

Treatment (including atezolizumab and chemotherapy, if applicable) will be discontinued in the event of disease recurrence while patient is receiving therapy.

### Paclitaxel

Paclitaxel should be administered as an IV infusion over a minimum of 1 hour or per institutional policy. Dose delays and reduction for toxicity are permitted. Paclitaxel should be administered after the atezolizumab infusion.

Paclitaxel Injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. Paclitaxel should be administered through an in-line filter with a microporous membrane that is not greater than 0.22 μm. Use of filter devices such as IVEX-2® filters, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of bis(2-ethylhexyl) phthalate (DEHP).

Sites should follow their institutional standard of care for determining the paclitaxel dose adjustments in the event of patient weight changes.

Premedication with corticosteroids should be administered as clinically indicated (see Section 4.5.2 for further guidance). Because systemic corticosteroids may attenuate the potential beneficial immunologic effects of treatment with atezolizumab, alternative agents, including antihistamines, should be considered when clinically feasible.

Refer to the local prescribing information for more details regarding the preparation and administration of paclitaxel.

### Doxorubicin

Patients may receive either dose-dense doxorubicin or dose-dense epirubicin per investigator's choice.

Doxorubicin may be given as an IV bolus over 3–5 minutes or as an infusion over 15–30 minutes. Dose delays and reduction for toxicity are permitted. Doxorubicin will be administered Q2W for four doses (dose-dense doxorubicin + cyclophosphamide [AC]) with G-CSF/GM-CSF support (see Section 4.5.1 for further guidance). Chemotherapy should be administered after the atezolizumab infusion.

Refer to the local prescribing information for details regarding the preparation and administration of doxorubicin.

### Epirubicin

Patients may receive either dose-dense doxorubicin or dose-dense epirubicin per investigator's choice.

Epirubicin may be given as an IV bolus over 3–5 minutes or as an infusion over 15–30 minutes. Dose delays and reduction for toxicity are permitted. Epirubicin will be administered Q2W for four doses (dose-dense EC) with G-CSF/GM-CSF support (see Section 4.5.1 for further guidance). Chemotherapy should be administered after the atezolizumab infusion.

Refer to the local prescribing information for details regarding the preparation and administration of epirubicin.

### Cyclophosphamide

Cyclophosphamide should be given as an IV bolus over 3–5 minutes or as an infusion in accordance with local standard of care. Dose delays and dose reductions for toxicity are permitted. Cyclophosphamide will be administered Q2W for four doses (as part of AC). Chemotherapy should be administered after the atezolizumab infusion.
Note: Oral cyclophosphamide is not permitted.

Chemotherapy-induced nausea and vomiting prophylaxis and treatment should be administered as clinically indicated (see Section 4.5.2 for further guidance). Because systemic corticosteroids may attenuate the potential beneficial immunologic effects of treatment with atezolizumab, alternative agents should be considered when clinically feasible.

Refer to the local prescribing information for details regarding the preparation and administration of cyclophosphamide.

**Pre-medications**

In general, chemotherapy supportive care should be administered per ASCO, EORTC, or ESMO guidelines or local standard of care. For further details regarding permitted therapies, see Section 4.5.1.

### 4.4.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, paclitaxel, doxorubicin, epirubicin, and cyclophosphamide) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

### 4.4.4 Post-Trial Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide atezolizumab or any other study treatments or interventions to patients who have completed the study.
The Sponsor may evaluate whether to continue providing atezolizumab 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

## 4.5 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

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

### 4.5.1 Permitted Therapy

Intraoperative RT as a boost at the time of primary surgery is acceptable.
Adjuvant radiotherapy is permitted as clinically indicated and according to guidelines included in the protocol (see Appendix 8). Radiotherapy can only be administered after chemotherapy is complete. Treatment with atezolizumab during adjuvant radiotherapy is permitted.

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

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, SARS-COV-2). Live attenuated vaccines are not permitted (see Section 4.5.4)
- Biphosphonates
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids (e.g., budesonide)
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Concomitant ovarian suppression with the use of luteinizing hormone releasing hormone agonist (LHRHa) during chemotherapy is allowed as a strategy to preserve ovarian function and fertility in premenopausal patients

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

Granulocyte colony-stimulating factor (e.g., filgrastim or pegfilgrastim) or GM-CSF treatment is permitted for patients receiving chemotherapy and is required during the doxorubicin/epirubicin + cyclophosphamide portion of chemotherapy. The primary prophylaxis should be administered per the ASCO, EORTC, or ESMO guidelines or per local standard practice (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011). This primary prophylaxis should be started within 3 days after the infusion of chemotherapy with doxorubicin/epirubicin + cyclophosphamide and not later than that.

For filgrastim as primary febrile neutropenia (FN) prophylaxis it is recommended to prescribe for at least five days of prophylactic filgrastim to be effective for preventing chemotherapy-induced FN (Clemons et al. 2020). Alternatively, a single dose of PEGylated G-CSF (pegfilgrastim) on Day 2 of each cycle may provide an effective, as well as a more convenient, option to daily filgrastim.

In case the local standard practice differs from international guidelines recommendation, prior contact with medical monitor is recommended.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 4.5.2 and Section 4.5.4) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or $H_2$-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and $\beta_2$-adrenergic agonists; see Appendix 7).

### 4.5.2 Cautionary Therapy for Atezolizumab-Treated Patients

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies may be used during the study at the discretion of the investigator.

### 4.5.3 Potential Drug Interactions with Chemotherapy

The chemotherapeutic agents used in this study are associated with potential drug interactions. The metabolism of paclitaxel is catalyzed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. Doxorubicin is a major substrate of CYP3A4 and CYP2D6 and P-glycoprotein (P-gp). Cyclophosphamide is a major substrate of CYP2B6. Epirubicin is metabolized extensively by the liver as well.

Caution should be exercised when paclitaxel is concomitantly administered with known inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin); inducers (e.g., rifampin, phenobarbital, phenytoin, St. John's Wort and carbamazepine); and substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin and

triazolam) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known inhibitors (e.g., gemfibrozil), inducers (e.g., rifampin), and substrates (e.g., repaglinide and rosiglitazone) of CYP2C8.

Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil). Caution should be exercised and concurrent use of doxorubicin with inhibitors and inducers of CYP3A4, CYP2D6, or P-gp should be avoided.

Similar cautions should be exercised with cyclophosphamide.

Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity; caution should be exercised when epirubicin is combined with agents that may affect hepatic function.

There is a moderate to high potential for drug-drug interactions with any medication that is metabolized by or strongly inhibits or induces these enzymes. Therefore, the medications listed above should be avoided when chemotherapy is being administered. If use of one of these medications is necessary, the risks and benefits should be assessed by the investigator prior to concomitant administration with chemotherapy. The Medical Monitor is available to advise as needed.

The lists of medications shown above are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP enzymes. In addition, the Medical Monitor is available to advise if questions arise regarding medications not listed above.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

### 4.5.4 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer other than those described in this study (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease recurrence is documented and the patient has discontinued study treatment, except as outlined below.

- Investigational therapy is prohibited during the study.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, and for 5 months after the last dose of study treatment.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Corticosteroids may be administered as clinically indicated or as otherwise described within the protocol (see Section 4.5.2 for further guidance).
- Hormonal contraceptives that inhibit ovulation should not be used during treatment and during the first 5 years after the diagnosis of breast cancer. The investigator should discuss with the patient other forms of adequate contraception (as listed in Section 4.1.1).
- During the study, initiation of contraception using hormone-releasing intrauterine devices is prohibited. Continuation of hormone-releasing intrauterine devices is allowed as long as these have been in-situ prior to study entry.
- Plinabulin, a new molecule being investigated for the reduction of chemotherapy-induced neutropenia is not allowed as a substitute to G-CSF/GM-CSF.

## 4.6 STUDY ASSESSMENTS

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

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

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that would preclude the visit, the visit should be scheduled on the nearest prior or following feasible date.

### 4.6.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). The ICFs 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 enrollment. The investigator will maintain a screening log to

record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 4.6.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, breast cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, breast cancer 1 (*BRCA1*), breast cancer 2 (*BRCA2*), partner and localizer of *BRCA2* (*PALB2*), *p53*, checkpoint kinase 2 (*CHEK2*; c.1100delC) gene mutation status (if known), and use of alcohol and drugs of abuse, will be recorded at baseline. TNBC history will include surgery and RT.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. The date of birth and race should be collected as per country regulation.

### 4.6.3 Physical Examinations

A complete physical examination, performed at screening and at the treatment discontinuation visit, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Special attention should be paid to cardiovascular symptoms (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs). Any abnormality identified at baseline should be recorded in the eCRF.

Limited, symptom-directed physical examinations should be performed at postbaseline visits (i.e., at Day 1 of every subsequent treatment cycle) and as clinically indicated with special attention to be paid to cardiovascular symptoms (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs). 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.

Height and weight will also be measured at baseline. Weight measurements will be repeated at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

### 4.6.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

At every clinic visit where study treatment is administered, vital signs should be measured within 60 minutes prior to the first infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

### 4.6.5 Radiographic Assessments

#### 4.6.5.1 Baseline Radiologic Exams

Patients with metastatic disease are ineligible to this study. Therefore, prior to randomization, patients must be evaluated according to local standards to exclude metastatic disease. Bilateral mammogram or breast magnetic resonance imaging (MRI) (within 6 months prior to randomization) is mandatory, unless there is no residual breast tissue. Radiological examinations, including X-ray, ultrasound, CT scan, bone scan, MRI and/or positron emission tomography (PET)/CT are permissible, as long as local guidelines are followed, and they were performed within 6 months prior to randomization.

#### 4.6.5.2 Radiologic Exams after Randomization

Patients randomized in this study should be submitted to radiological examinations as per national or international guidelines in order to assess distant disease recurrence status during study treatment and follow-up. All radiological examinations, including X-ray, ultrasound, CT scan, bone scan, MRI and/or PET/CT are permissible, as long as they are performed according to guidelines. Patients with any remaining breast tissue should have a mammogram/breast MRI at least annually from the date of the mammogram/breast MRI performed at screening/surgery and as clinically indicated, based on findings from physical examinations.

### 4.6.6 Disease Follow-Up and Confirmation of Disease Recurrence

All patients must be followed to assess disease recurrence, second primary cancer, and survival. Disease recurrence or status based on all available clinical assessments should be evaluated and documented every 3 months during study treatment and for up to 3 years after randomization; at intervals of every 6 months from 3–5 years after randomization; and annually thereafter until the end of the study (see Section 3.2).

The diagnosis of a breast cancer recurrence or second primary tumor should be confirmed histologically whenever clinically possible.

Some patients may experience a suspicious recurrence that leads to death relatively quickly, without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such cases.

The earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence. The recurrence of disease has to be backdated to the date of the first diagnosis of lesion (i.e., an objective finding), not to the date of occurrence of the first symptom.

For example, a patient presenting with abdominal pain is found to have a possible lesion on liver CT scan of uncertain significance. If a subsequent CT scan confirms disease progression, the date of the first diagnostic CT scan should be taken as the date of recurrence (not the date of presentation with abdominal pain). Thus, the actual date of relapse of disease is the time of first appearance of a suspicious lesion (in a radiological procedure in this case), later proven to be a definitive recurrence or metastasis.

Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. Patients who have a diagnosis of in situ breast disease or second malignancies not requiring systemic therapy should be maintained on a regular follow-up schedule wherever possible in order to fully capture any subsequent recurrent invasive disease events. Patients who have a diagnosis of secondary malignancies requiring systemic therapy should be followed-up similarly to patients who experience disease recurrence.

The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events on follow-up are provided in Table 3.

**Table 3 Definitions of and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Events on Follow-Up**

| | | |
|---|---|---|
| **a) Local invasive recurrence** | Ipsilateral breast after previous lumpectomy | • Defined as evidence of invasive tumor (except DCIS and LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis.<br>• Confirmed by positive histology or cytology |
| | Ipsilateral after previous mastectomy | • Defined as evidence of invasive tumor in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle, and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or extending across the midline will be considered as evidence of local recurrence.<br>• Confirmed by positive histology or cytology |

## Table 3 Definitions of and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Events on Follow-Up (cont.)

| | |
|---|---|
| **b) Regional recurrence** | • Defined as the development of tumor in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes, or supraclavicular lymph nodes as well as extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumor in the opposite breast.<br>• Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT or MRI if no biopsy was performed) |
| **c) Distant recurrence** | • Defined as evidence of tumor in all areas, with the exception of those described in a) and b) above<br>• Confirmed by the following criteria:<br>– Skin, subcutaneous tissue, and lymph nodes (other than local or regional)<br>Positive cytology, aspirate or biopsy, OR<br>Radiological (CT scan, MRI, PET, or ultrasound) evidence of metastatic disease<br>– Bone<br>X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR<br>Bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), OR<br>Biopsy proof of bone metastases or cytology<br>– Bone marrow<br>• Positive cytology or histology or MRI scan<br>– Lung<br>X-ray, CT scan or PET scan evidence of multiple pulmonary nodules consistent with pulmonary metastases<br>Positive cytology or histology (practically rarely performed with the exception of solitary nodules)<br>NOTE: For solitary lung lesions, cytological or histological confirmation should be obtained in case of diagnostic doubt. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy.<br>– Liver<br>Radiologic evidence consistent with liver metastases, OR<br>Liver biopsy or fine-needle aspiration<br>NOTE: If radiological findings are not definitive (especially with solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained if possible to document stability or progression.<br>– Central nervous system<br>• Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR<br>Biopsy or cytology in case of inconclusive imaging (e.g., for a diagnosis of meningeal involvement) and depending on the general status of the patient additional investigations (including cytology of the cerebrospinal fluid). |

**Table 3 Definitions of and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Events on Follow-Up (cont.)**

| | |
|---|---|
| **d) Contralateral invasive breast cancer** | • Confirmed by positive cytology or histology |
| **e) Second primary malignancy (breast or other cancer)** | • Any positive diagnosis of a second (non-breast) primary cancer other than basal or squamous cell carcinoma of the skin, or CIS of any site will not be included in the iDFS primary endpoint.<br>• LCIS and DCIS of the breast and myelodysplastic syndrome are not considered progression events.<br>• All second primary malignancies are to be reported whenever they occur during the study. The diagnosis of a second primary cancer must be confirmed histologically.<br><br>NOTE: Patients diagnosed with a second primary malignancy not requiring systemic therapy (i.e., chemotherapy, hormonal therapy, targeted therapy, etc.) and with no evidence of breast cancer recurrence will remain in the study. They should continue with study treatment and/or should continue to attend visits as per regular follow-up according to the protocol and schedule of activities, if considered by the investigator to be in the patient's best interest, whenever possible. Patients who have a diagnosis of second primary malignancies requiring systemic therapy should be followed-up similarly to patients who experience disease recurrence. |
| **f) Death from any cause** | • Any death occurring without prior breast cancer recurrence or second (non-breast) malignancy is considered an event for the following endpoints: iDFS, DFS, and OS. |
| **g) Other noteworthy events** | The following events should be recorded on the follow-up eCRF:<br>• Ipsilateral and contralateral LCIS<br>• Ipsilateral and contralateral DCIS<br>• Carcinoma in situ of the cervix<br>• Basel or squamous cell carcinoma of the skin<br><br>NOTE: These events are not considered recurrent disease for iDFS but must be recorded until end of study. Ipsilateral and contralateral DCIS are considered events for the endpoint of DFS. |

CIS = carcinoma in situ; CT = computed tomography; DCIS = ductal carcinoma in situ; DFS = disease-free survival; eCRF = electronic Case Report Form; iDFS = invasive disease-free survival; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; OS = overall survival; PET = positron emission tomography.

### 4.6.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis as outlined in the schedule of activities (see Appendix 1 and Appendix 2) and as clinically indicated:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)

- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH, and, if clinically indicated or considered standard of care, bicarbonate/total $CO_2$, lipase and amylase
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine
- Viral serology
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA
  - If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and, if HCV antibody test is positive, HCV RNA
  - If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Pregnancy test
  - All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor for analysis (see Appendix 2):

- Serum samples for analysis of autoantibodies: anti-nuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Serum samples for atezolizumab PK analysis through use of a validated assay
- Serum samples for assessment of anti-drug antibodies (ADAs) to atezolizumab through use of a validated assay
- Blood and plasma samples for exploratory research on biomarkers

- Tumor tissue sample collected at baseline for determination of PD-L1 expression; for determination of HER2, ER, and PgR negativity; and for exploratory research on biomarkers
  - A representative FFPE tumor specimen from surgical resection in a paraffin block (preferred) or approximately 25 slides (minimum of 20 slides) containing unstained, freshly cut (PD-L1 epitope stability is 60 days from sectioning), serial sections must be submitted along with an associated pathology report prior to study enrollment. After signing of the ICF, retrieval of a tumor sample can occur outside the 28-day screening period.
  - Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture in the surgical tumor tissue material. Tumor tissue should be of good quality based on total and viable tumor content. The only acceptable samples are surgical resections.
  - Tissue should meet the tumor tissue requirements described in the eligibility criteria. Remaining FFPE tumor tissue for enrolled patients will be returned to the site upon request. Left over tissue from FFPE for patients who are not enrolled in the study will be returned to the site no later than 6 weeks after eligibility determination. Slides will not be returned.
  - *Analysis of PD-L1 expression will be performed using the VENTANA PD-L1 (SP142) Assay which may be considered investigational per local regulations.*
- FFPE tumor tissue sample collected at the time of recurrence, if deemed clinically feasible by the investigator, for exploratory research on biomarkers
  - Biopsies should be performed within 40 days after recurrence and prior to the next anti-cancer therapy. Acceptable samples include those from resections, core-needle biopsies (at least two cores preferred, or at least 20 slides), or excisional, incisional, punch, or forceps biopsies. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, bone metastases, and lavage samples are not acceptable.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocytes, T-cell receptor repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of somatic mutations, and use of next generation sequencing (NGS).

NGS will be performed by Foundation Medicine in the samples collected at disease relapse. The investigator may obtain an NGS report through Foundation Medicine's Web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet testing criteria.

Depending on local regulations, NGS analyses may not be available to all participating countries.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.6.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK analysis and/or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Leftover blood, plasma, serum, and tumor samples collected for exploratory analysis during the study will be destroyed no later than 15 years after the final Clinical Study Report has been completed.
- For patients from China, all samples and data will be handled in accordance with the Human Genetic Resource Administration of China (HGRAC) requirement and the pertinent HGRAC approval letter for this study.

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.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law, with the exception of the NGS report for the samples obtained at disease relapse. The aggregate results of any conducted research will be available in accordance with the effective ALEXANDRA/IMpassion030 Publication and Presentation policy.

### 4.6.8 Electrocardiograms

A 12-lead ECG is required at screening and when clinically indicated. The ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes or as per local practice prior to ECG recording.

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.

### 4.6.9 Echocardiograms or Multiple-Gated Acquisition Scans

The LVEF will be assessed by echocardiography (preferably) or MUGA scan at specified timepoints, as outlined in the schedule of activities (see Appendix 1) and as clinically indicated. Patients should be reassessed with the same technique used for baseline cardiac evaluation throughout the study.

### 4.6.10 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through use of the following instruments: EORTC QLQ-C30; item GP5 of the FACT-G quality-of-life instrument; and the EuroQoL 5-Dimension, 5-Level (EQ-5D-5L) questionnaire.

Official versions of the PRO instruments in booklet format, translated as required in the local language, will be distributed by the investigator staff and completed on paper in their entirety by the patient at the investigational site. To ensure instrument validity and that data standards meet health authority requirements, questionnaires must be completed by the patient at the start of the clinic visit before discussion of the patient's health state, laboratory results, or health record; before administration of study treatment; and/or prior to the performance of any other study assessments that could bias the patient's responses. If the patient is unable to complete the measure on her or his own, interviewer assessment is allowed but may only be conducted by a member of the clinic staff who reads the questionnaire items to the patient verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the respondent's initials, study patient number and date, and time of completion recorded in compliance with good clinical practice. Sites will enter patient responses to the PRO questionnaires into the electronic data capture (EDC) system.

All patients will begin completion of the questionnaires with the EORTC QLQ-C30, followed by the FACT-G single item GP5, and then the EQ-5D-5L at timepoints corresponding with in-clinic visits; both while receiving study treatment and after treatment discontinuation. See Appendix 1 for the frequency and timing of PRO assessments.

#### 4.6.10.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; see Appendix 3). It consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales.
The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

#### 4.6.10.2 FACT-G Single Item GP5

The FACT-G instrument Version 4 (see Appendix 4) is a validated and reliable 27-item questionnaire comprised of 4 subscales that measure physical (7 items), social/family (7 items), emotional (6 items) and functional well-being (7 items), and is considered appropriate for use with patients with any form of cancer (Cella et al. 1993; Webster et al. 1999). In this study, the single-item GP5 ("I am bothered by side effects of treatment") from the physical well-being subscale of the FACT-G has been selected for individual item analysis to document the level of bother of symptoms on patient's lives. Patients will assess how true the statement "I am bothered by side effects of treatment" has been for them in the previous 7 days on a five-point scale (0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; 4, very much).
The single-item GP5 from the FACT-G takes less than a minute to complete.

#### 4.6.10.3 EQ-5D-5L

The EQ-5D-5L, is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 5). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health utility. Utility scores will be used in this study for informing pharmacoeconomic evaluations. As such, the utility results will not be included in the Clinical Study Report. The EQ-5D-5L takes approximately 3 minutes to complete.

### 4.6.11 Optional Research Project Biological Samples

Optional research project biological samples (RPBS) will be stored in a centrally administered facility, the study repository, 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 RPBS 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.

The RPBS will be collected from patients who give specific consent to participate in this optional research. The RPBS will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease recurrence
- 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

#### 4.6.11.1 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of RPBS is contingent upon the review and approval of the exploratory research and the RPBS portion of the ICF by each site's IRB/Ethics Committee and, if applicable, an appropriate regulatory body. If a site has not been granted approval for the collection of RPBS, this section of the protocol (Section 4.6.11) will not be applicable at that site.

#### 4.6.11.2 Sample Collection

The following RPBS will be stored in the study repository and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab or diseases:

- Whole blood sample for DNA isolation collected from patients who have consented to optional RPBS collection at Cycle 1, Day 1 (see Appendix 2)

  If, however, the genetic blood RPBS is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

  Collection of whole blood will enable the evaluation of single nucleotide polymorphisms in genes associated with immune biology including, but not restricted to, the target and pathway associated genes such as PD-L1, PD-1, and B7-1 as well as interleukin-8, interleukin-6, and related cytokines. The sample may be processed using techniques such as kinetic polymerase chain reaction (PCR) and DNA sequencing.
- Leftover blood, plasma, and tumor tissue samples (with the exception of leftover screening tissue from FFPE blocks, which will be returned to sites upon request) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline mutations or somatic mutations via WGS, whole exome sequencing (WES), NGS, or other genomic analysis methods.

The samples described above will be stored under the guardianship of the Breast International Group (BIG) on behalf of the SC in the study repository that is independent from any of the Parties. Any use of and access to the RPBS will be governed by the SC.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies upon agreement of the SC of the study. 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, refer to the laboratory manual.

The RPBS are to be stored until they are no longer needed or until they are exhausted. However, the RPBS storage period will be in accordance with the IRB/Ethics Committee-approved ICF and applicable laws (e.g., health authority requirements).

#### 4.6.11.3 Confidentiality

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

Patient medical information associated with RPBS is confidential and may be disclosed to third parties only as permitted by the ICF (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 of RPBS, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective ALEXANDRA/IMpassion030 Publication and presentation Policy.

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

#### 4.6.11.4 Consent to Participate in Research Project Biological Sample Collection

The ICF will contain a separate section that addresses RPBS. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in RPBS collection. Patients will be told that they are free to

refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RPBS. 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, in the eCRF.

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

#### 4.6.11.5 Withdrawal of Consent for Research Project Biological Sample Collection

Patients who give consent to provide RPBS have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RPBS have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RPBS Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the eCRF. If a patient wishes to withdraw consent to the testing of his or her RPBS samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study BIG 16-05/AFT-27/WO39391 does not, by itself, constitute withdrawal of consent for RPBS collection. Likewise, a patient's withdrawal of consent for RPBS collection does not constitute withdrawal from Study BIG 16-05/AFT-27/WO39391.

#### 4.6.11.6 Monitoring and Oversight of RPBS

RPBS will be tracked in a manner consistent with Good Clinical Practice (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 ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in RPBS collection for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/Ethics Committee review, and health authority inspections by providing direct access to source data and documents related to the RPBS.

## 4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.7.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (atezolizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any adverse event that requires study treatment discontinuation per the guidelines in Section 5.1 and the Atezolizumab Investigator's Brochure
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Confirmation of disease recurrence

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. For patients (in both Arm A and Arm B) who discontinue study treatment prematurely (see Section 4.7.2) due to an adverse event, every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until an outcome can be reported, including during the follow-up period. Additional tests can be performed, if needed, according to standard medical practice.

### 4.7.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time if it's in the patient's best interest. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent

  From study treatment and/or procedures (i.e., partial withdrawal)

  From survival follow-up (patient does not want to be contacted)
- Study termination or site closure
- Investigator or Sponsor determines it is in the best interest of the patient
- Severe/major non-compliance (e.g., missed doses and/or missed visits)

  The Medical Monitor is available to advise as needed, before removing a patient for non-compliance.

Study treatment discontinuation by itself is not a reason for patient discontinuation from study. Patients should continue to have follow-up information collected and submitted following treatment discontinuation if at all possible.

Every effort should be made to obtain information on patients who withdraw from the study treatment and/or assessments but have agreed to be contacted for further information (i.e., partial withdrawal). Partial withdrawal from the study, with consent to allow collection of information regarding disease recurrence, survival status, and reportable toxicity, should be documented in both the medical records and in the eCRF (i.e., the patient accepted to be contacted for collection of these data despite withdrawing consent from the study treatment and/or procedures).

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

### 4.7.3 Study Discontinuation

The Academic partners and Sponsor have 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 as determined by the Academic partners and Sponsor.

Such decisions shall be communicated promptly, in order to allow the termination procedure to be properly followed. The Academic partners and Sponsor will also notify the investigator if the study is terminated early.

### 4.7.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab and paclitaxel, doxorubicin/epirubicin, and cyclophosphamide in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1–5.1.5,). Guidelines for management of patients who experience specific adverse events are provided in Table 5 (see Section 5.1.6).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Section 4.1) and close monitoring of patients during the study as indicated below. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

An IDMC (see Section 3.1.1) has also been incorporated into the trial design to periodically review aggregate safety data.

The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

### 5.1.1 Risks Associated with Atezolizumab

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

involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH). See Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for managing patients who experience anticipated adverse events are provided in Appendix 9.

### 5.1.2 Risks Associated with Paclitaxel

Paclitaxel is known to cause myelosuppression, alopecia, peripheral neuropathy, myalgia, arthralgia, nausea, and vomiting. Less commonly reported adverse events are hypersensitivity reactions, infections, bleeding, diarrhea, mucositis, liver function test elevations, injection site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other ECG abnormalities, syncope, and venous thrombosis.

Refer to the paclitaxel Summary of Product Characteristics (package insert) for more details regarding the full safety profile of paclitaxel, including boxed warnings and contraindications.

### 5.1.3 Risks Associated with Doxorubicin

Doxorubicin is known to cause serious cardiomyopathy; arrhythmias, including life-threatening arrhythmias; increased incidence of secondary acute myelogenous leukemia and myelodysplastic syndrome; extravasation and tissue necrosis; infection; severe myelosuppression resulting in serious infection, septic shock, angioedema of the eyelids and tongue and respiratory impairment need for transfusions, phlebosclerosis; hospitalization and death; tumor lysis syndrome; radiation sensitization and radiation recall; secondary acute myeloid leukemia, embryo fetal toxicity; alopecia, vomiting, nausea, and other gastrointestinal effects.

Refer to the doxorubicin Summary of Product Characteristics (package insert) for more details regarding the full safety profile of doxorubicin, including boxed warnings and contraindications.

#### 5.1.3.1 Cardiomyopathy

Patients treated with anthracyclines such as doxorubicin are at risk of developing cumulative dose-related myocardial damage. Significant cardiac events, including acute heart failure and LVEF of $<40\%$, have been observed in clinical trials of anthracyclines. Cardiomyopathy may develop during treatment or up to several years after completion of treatment. There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide.

Patients must meet specified LVEF requirements to be included in this study (see Section 4.1.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO or MUGA scans as described in Section 4.6.9 and the schedule of activities (see Appendix 1).

### 5.1.4 Risks Associated with Epirubicin

Epirubicin is known to cause serious cardiomyopathy; arrhythmias, including life-threatening arrhythmias; increased incidence of secondary acute lymphocytic leukemia and secondary acute myelogenous leukemia; extravasation and tissue necrosis; severe myelosuppression resulting in serious infection, septic shock, need for transfusions, hospitalization and death; tumor lysis syndrome; radiation sensitization and radiation recall; embryo fetal toxicity; alopecia; hyperuricemia; dizziness; hot flashes; and anorexia, dehydration, vomiting, nausea, and other gastrointestinal effects.

Refer to the epirubicin Summary of Product Characteristics (package insert) for more details regarding the full safety profile of epirubicin, including boxed warnings and contraindications.

#### 5.1.4.1 Cardiomyopathy

Patients treated with anthracyclines such as epirubicin are at risk of developing cumulative dose-related myocardial damage. Significant cardiac events, including acute heart failure and LVEF of $<$40%, have been observed in clinical trials of anthracyclines. Cardiomyopathy may develop during treatment or up to several years after completion of treatment. There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide.

Patients must meet specified LVEF requirements to be included in this study (see Section 4.1.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO or MUGA scans as described in Section 4.6.9 and the schedule of activities (see Appendix 1).

### 5.1.5 Risks Associated with Cyclophosphamide

Cyclophosphamide has been associated with myelosuppression sometimes leading to severe immunosuppression and infections that can be serious and sometimes fatal; hemorrhagic cystitis, pyelitis, ureteritis and hematuria; myocarditis, myopericarditis, pericardial effusion, arrhythmias and congestive heart failure; pulmonary toxicity including pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease

leading to respiratory failure; secondary malignancies; veno-occlusive liver disease; embryo-fetal toxicity; alopecia; cecitis, nausea, vomiting, and diarrhea.

Refer to the cyclophosphamide Summary of Product Characteristics (package insert) for more details regarding the full safety profile of cyclophosphamide, including boxed warnings and contraindications.

### 5.1.6 Management of Patients Who Experience Specific Adverse Events

There will be no dose modifications for atezolizumab in this study. Missed doses of atezolizumab due to interruption of treatment for any reason during the chemotherapy, or after, will not be made up (i.e., atezolizumab treatment cannot exceed 1 year calculated from date of the first atezolizumab administration).

For guidelines regarding the management of atezolizumab-specific adverse events, please see Appendix 9.

Study treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. In case of toxicities attributed to atezolizumab, chemotherapy may be continued independently of atezolizumab if there is no contraindication. Atezolizumab may be restarted when the conditions for retreatment have been met. When atezolizumab is restarted, the infusions should remain synchronized and aligned with the chemotherapy schedule and it should be administered at a scheduled atezolizumab visit.

In case of unacceptable toxicity attributed to chemotherapy in Arm A, atezolizumab should be interrupted and restarted together with chemotherapy if there is no contraindication. If paclitaxel is to be discontinued, patients can proceed to AC or dose-dense epirubicin + cyclophosphamide (EC) at the discretion of the investigator. In cases where chemotherapy is withdrawn, atezolizumab may be restarted based on the investigator's benefit–risk assessment. The Medical Monitor is available to advise as needed.

Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

For guidelines regarding the management (i.e., dose modification and treatment interruption rules) of doxorubicin/epirubicin or cyclophosphamide-associated toxicities, please refer to the respective local prescribing information for each agent.

For paclitaxel-specific management guidelines, please see Table 4 below. For further guidance, please refer to local prescribing information for paclitaxel.

**Table 4 Dose Levels for Paclitaxel (Weekly Dose)**

| | Dose Level 0 (Starting Dose) | Dose Level −1 | Dose Level −2 |
|---|---|---|---|
| Paclitaxel weekly dose | 80 mg/m$^2$ | 64 mg/m$^2$ [b] | Discontinue [a] |

[a] Switching to an alternative taxane (e.g., docetaxel or nab-paclitaxel) may be considered in exceptional circumstances if deemed appropriate by the investigator and discussed with the Medical Monitor.

[b] If the paclitaxel dose has been lowered due to an adverse event it should remain at the lower dose for the remainder of treatment.

## Table 5 Guidelines for Management of Patients Who Experience Paclitaxel-Specific Adverse Events

| Event | Action to Be Taken |
|---|---|
| **Infusion-Related Reactions and Anaphylaxis** | |
| | • For Grade ≤ 3 paclitaxel hypersensitivity reaction, continuation of paclitaxel is at the investigator's discretion. Patient should be managed per local standard of care.<br>• For Grade 4 paclitaxel hypersensitivity reaction, paclitaxel must be permanently discontinued. Patient should be managed per local standard of care.<br>• For anaphylaxis precautions, see Appendix 7 |
| **Hepatotoxicity: Bilirubin or AST/ALT or ALP Increased (Grades 2–4)** | |
| Grade 2 or 3 | • Hold paclitaxel until bilirubin returns to baseline grade and AST/ALT and ALP have recovered to Grade 1 or better (check weekly).<br>• Resume subsequent cycle with decrease of paclitaxel by one dose level |
| Grade 4 | • Discontinue paclitaxel. |
| **Neurologic Disorders** | |
| Neuropathy, Grade 2 | • Withhold paclitaxel if persistent > 7 days or caused the next dose to be delayed.<br>• Resume paclitaxel if event resolves to Grade 1 or better and decrease by one dose level.<br>• If persistent after 3 weeks of withholding paclitaxel, discontinue paclitaxel. |
| Neuropathy, Grade 3 or 4 | • If first episode, withhold paclitaxel. If persistent for > 7 days or caused the next dose to be delayed, resume paclitaxel if event resolves to Grade 1 or better on Day 1 of the next dose and decrease by one dose level.<br>• If second episode, discontinue paclitaxel permanently. |
| **Hematologic Toxicity** | |
| Neutrophil count decreased, Grade 3, or 4 | • If resolves prior to next treatment dose, maintain paclitaxel dose.<br>• If requires a delay in the administration of next treatment dose:<br>– Hold paclitaxel until ANC ≥ 1000 cells/mm$^3$.<br>If recovery takes 1–3 weeks, maintain dose and add G-CSF.<br>If receiving G-CSF and recovery takes 1 week, maintain dose; if recovery takes 2–3 weeks, decrease one dose level. |

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

**Table 5 Guidelines for Management of Patients Who Experience Paclitaxel-Specific Adverse Events (cont.)**

| Event | Action to Be Taken |
|---|---|
| **Hematologic Toxicity (cont.)** | |
| Platelet count decreased, Grade 2 or 3 | • If resolves prior to next treatment dose, maintain paclitaxel dose.<br>• If requires a delay in the administration of next treatment dose:<br>– Hold paclitaxel until platelets ≥ 75,000 cells/mm$^3$. If recovery takes 1 week, maintain paclitaxel dose. If recovery takes 2–3 weeks, decrease one dose level. |
| Grade 4 | • Hold paclitaxel until platelets ≥ 75,000 cells/mm$^3$.<br>• Decrease paclitaxel one dose level. |

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor.

## 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 (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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 (see 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 treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

Severity and seriousness need to be independently assessed for each 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 learning of the event; see Section 5.4.2 for reporting instructions).

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7) and based on the following observations:
  - Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
  - Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice
- 
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenza-like illness, HLH and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade $\geq 2$ cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

### 5.2.4 Selected Adverse Events

Additional data will be collected for the selected adverse events in the following sections.

#### 5.2.4.1 Cardiac, General

Symptomatic left ventricular systolic dysfunction should be reported as a serious adverse event. If the diagnosis is heart failure, it should be reported as such and not in terms of the individual signs and symptoms thereof.

Heart failure should be graded according to the NCI CTCAE (v5.0) for "heart failure" (Grade 2, 3, 4, or 5) and in addition according to the NYHA classification.

Heart failure occurring during the study and post-study must be reported and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death (see Section 5.6).

#### 5.2.4.2 Asymptomatic Ejection Fraction Decrease

Asymptomatic declines in LVEF should generally not be reported as adverse events because LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF $\geq$10 percentage points from baseline to an LVEF $<$50% must be reported as an adverse event with the term ″ejection fraction decreased as per NCI CTCAE (v5.0), and, in addition, a comment in the adverse events comments field should confirm that this was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment delay or leading to discontinuation of atezolizumab, paclitaxel, doxorubicin/epirubicin, or cyclophosphamide must also be reported.

## 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 5.4–5.6.

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 (see Section 5.3.3), and causality (see 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 treatment, 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 treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting 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 for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

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

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

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

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

[d] Grade 4 and 5 events, not specifically listed in the NCI CTCAE, 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 study treatment (e.g., IMP), indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

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

**Table 7 Causal Attribution Guidance**

| Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment? | |
|---|---|
| YES | There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, 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 study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge. |
| NO | An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (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 study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment). |

For patients receiving combination therapy, causality should be assessed individually by the investigator for each protocol-mandated therapy.

### 5.3.5 Procedures for Recording Adverse Events

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

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

#### 5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

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

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

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

eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 9.

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events (see 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, dizziness and the consequent fracture should be reported separately on the eCRF.
- If neutropenia is accompanied by an 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 × 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

### 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

### 5.3.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

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

#### 5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to recurrence and progression of breast cancer should be recorded on the eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must also be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An IDMC will monitor the frequency of deaths from all causes.

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

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

#### 5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study or clinically significant as per the inclusion/exclusion criteria of this study. Such conditions should be recorded on the 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 Recurrence of TNBC

Events that are clearly consistent with the expected recurrence or pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. 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., inpatient 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 treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study for cosmetic or reconstructive surgery or 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 recurrence/progression of the underlying cancer

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

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

#### 5.3.5.12 Reporting Requirements for Cases of Accidental Overdose or Medication Error

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
- In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF, see Section 4.5.2. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 4.5.2). For atezolizumab, paclitaxel, doxorubicin, epirubicin, and cyclophosphamide, adverse events associated with special situations should be recorded as described below for each situation:

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

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the “Accidental overdose” and “Medication error” boxes.

In addition, all special situations associated with atezolizumab, paclitaxel, doxorubicin, epirubicin, and cyclophosphamide, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

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

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

#### 5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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/Ethics Committee.

### 5.4.1 Emergency Medical Contacts

**Roche/Medical Monitor Contact Information**

Medical Monitor: [redacted] M.D., PhD
Mobile Telephone No.: [redacted]

Medical Monitor: [redacted] M.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 Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. 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 Treatment Initiation

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the 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 serious adverse events that occur > 90 days after the last dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the ICF to immediately inform the investigator if they become pregnant during the treatment period or within 5 months after the last dose of atezolizumab, or 6 months after the last dose of paclitaxel or doxorubicin/epirubicin, or 12 months after the last dose of cyclophosphamide, whichever is later. A 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 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 eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the treatment period or within 6 months after the last dose of paclitaxel or doxorubicin/epirubicin, or 12 months after the last dose of

cyclophosphamide, whichever is later. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### 5.4.3.3 Abortions

A spontaneous abortion of a pregnancy for which the onset date falls in the reporting requirements mentioned in Section 5.4.3.1 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; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as 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; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

#### 5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment 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; see Section 5.4.2).

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each 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, or the patient withdraws consent, or the patient is dead. Every effort

should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study treatment period and up to treatment discontinuation visit, 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, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting 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.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, Ethics Committees, 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 following reference documents:Atezolizumab Investigator's Brochure

- EU- Summary of Product Characteristics for paclitaxel, doxorubicin/epirubicin, and cyclophosphamide

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 monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis population for efficacy is the ITT population, defined as all randomized patients. Patients will be assigned to the treatment group to which they were randomized.

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

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

The primary analysis population for safety is the safety-evaluable population, defined as all patients who received at least one dose of study medication. Patients will be assigned to treatment groups as treated, and all patients who received any dose of atezolizumab will be included in the atezolizumab treatment group.

## 6.1 DETERMINATION OF SAMPLE SIZE

The final analysis of the primary endpoint of iDFS will take place when approximately *390 iDFS events* (approximately *17% of the planned enrollment* of 2300 patients experiencing an iDFS event; see Section 6.4.1) have occurred in the ITT population. This sample size is computed on the basis of the following assumptions:

- Primary statistical test: two-sided, stratified log-rank test at the 0.05 significance level in the ITT population
- Approximately 80% power for iDFS
- A hazard ratio (HR) of 0.75
- Annual hazard rates of 0.047, 0.108, 0.035, 0.038, 0.029, and 0.014 in Years 1, 2, 3, 4, 5–6, and 7 and thereafter are assumed for the T-AC/EC arm based on the adjuvant TNBC trials ECOG E1199 (Sparano et al. 2015), BEATRICE (Cameron et al. 2013), and IBCSG 22-00 (Colleoni et al. 2016)

- Based on the piecewise hazard rates given above for the control arm, and the assumed HR of 0.75 (thus reducing the risk of an iDFS event by 25% at each piecewise interval), the 3-year iDFS rate (probability of not having any iDFS event in the first 3 years) will be 82.7% in the T-AC/EC arm and 86.7% in the atezolizumab + T-AC/EC arm
- 2.5% annual loss to follow-up for iDFS
- *Interim analyses* for iDFS in the ITT population, see Section 6.9.1

Accrual is projected to occur over approximately 51 months. The required number of iDFS events *for the final analysis* in the ITT population is projected to occur *77 months* after first patient in. Also, on the basis of these assumptions, an observed HR of 0.81 or better will result in a statistically significant difference between the treatment arms (i.e., HR = 0.81 will be the minimally detectable difference for the analysis; this corresponds to an improvement in 3-year iDFS from 82.7% in the T-AC/EC arm to 85.7% in the atezolizumab + T-AC/EC arm).

The study duration for the secondary endpoint, OS, was determined on the basis of the number of events required to demonstrate efficacy with regard to OS. A total of *approximately 299 deaths* are required to achieve 80% power at a two-sided alpha level of 5% to detect an HR of 0.72, corresponding to an improvement in 5-year OS rate from 84% in the T-AC/EC arm to 88.2% in the atezolizumab + T-AC/EC arm assuming a constant hazard. An annual loss to follow-up of 2.5% and *three* interim analyses of OS are assumed. The final analysis of OS is planned to take place approximately 7 years after the first patient has been randomized.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations including major deviations of inclusion/exclusion criteria, and discontinuation from the study will be summarized by treatment arm for all randomized patients. The reasons for study discontinuation will be tabulated.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (in particular, stratification variables) will be summarized by treatment arm for all randomized patients. Continuous variables will be summarized with use of means, standard deviations, medians, ranges, and inter-quartile ranges. Categorical variables will be summarized by proportions.

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

## 6.4 EFFICACY ANALYSES

The primary and secondary efficacy endpoints are described in Table 1 and Table 3. The primary and secondary efficacy analyses will include all randomized patients

(except for iDFS in the subpopulation with PD-L1-selected tumor status [IC1/2/3] and for iDFS in the subpopulation with node-positive disease), with patients grouped according to their assigned treatment.

### 6.4.1 Primary Efficacy Endpoint: Invasive Disease-Free Survival

The primary efficacy variable is iDFS, defined as the time between randomization and date of first occurrence of an iDFS event as described in Table 1 and Table 3. Data from patients who have not had an event at the time of data analysis will be censored on the date on which they are last known to be alive and event free, on or before the clinical data cutoff date of the respective analysis.

Patients with no postbaseline information will be censored on the date of randomization.

The log-rank test, stratified by the protocol-defined stratification factors, will be used to compare iDFS between the two treatment arms. The HR for iDFS will be estimated with use of a stratified Cox proportional hazards model. The Kaplan-Meier approach will be used to estimate 3-year iDFS rates, and corresponding 95% CIs for each treatment arm will be used to describe iDFS in addition to the HR.

### 6.4.2 Secondary Efficacy Endpoints

To adjust for multiple statistical testing of the key secondary efficacy endpoints, thereby controlling the overall type I error rate at a two-sided significance level of 5%, the fixed-sequence testing procedure will be used. These endpoints will be tested at a two-sided significance level of 0.05 in the following order:

- iDFS in the subpopulation with PD-L1-selected tumor status (IC1/2/3)
- iDFS in the subpopulation with node-positive disease
- OS
- iDFS, including second primary non-breast invasive cancer (except for non-melanoma skin cancers and in situ carcinoma of any site) as an iDFS event
- Recurrence-free interval (RFI)
- Distant recurrence-free interval (DRFI)
- DFS

The testing hierarchy will place the primary endpoint, iDFS in the ITT population, at the top of the hierarchy (i.e., no alpha-splitting between iDFS and any other endpoint[s]).

Secondary endpoints not included in the fixed sequence testing procedure including PROs of function (role, physical) and HRQoL are also described in Section 6.4.2.8.

#### 6.4.2.1 iDFS in the Subpopulation with PD-L1-Selected Tumor Status (IC1/2/3)

iDFS is defined in an analogous manner to the primary endpoint and will be analyzed with the same methodology in the subpopulation of patients with PD-L1-selected tumor status (IC1/2/3). The stratification factors are axillary nodal status (0 vs. 1–3 vs. ≥4 positive lymph nodes) and surgery (breast conserving vs. mastectomy).

#### 6.4.2.2 iDFS in the Subpopulation with Node-Positive Disease

iDFS is defined in an analogous manner to the primary endpoint and will be analyzed with the same methodology in the subpopulation of patients with node-positive disease.

#### 6.4.2.3 Overall Survival

OS is defined as the time from randomization to the date of death due to any cause. Patients who are not reported as having died at the time of the clinical data cutoff date will be censored at the date when they were last known to be alive. Patients who do not have information after baseline will be censored at the date of randomization.
The OS will be analyzed with the use of the same methodology as specified for iDFS.

#### 6.4.2.4 iDFS, including Second Primary Non-Breast Cancer

iDFS is defined in an analogous manner to the primary endpoint with the addition of second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) and will be analyzed with the same methodology.

#### 6.4.2.5 Recurrence-Free Interval

RFI is defined as the time from randomization to the first occurrence of any recurrence (local, regional [including invasive ipsilateral tumor and invasive locoregional tumor], or distant), as determined by investigators.

Patients without an event at the time of clinical cutoff for the analysis will be censored at the last date the patient was known to be alive and event free. Patients without an event who died will be censored at the date of death. Patients with no postbaseline information will be censored on the date of randomization. The RFI will be analyzed with the same methodology as specified for iDFS.

#### 6.4.2.6 Distant Recurrence-Free Interval

DRFI is defined as the time from randomization to distant breast cancer recurrence. The censored data will be handled in the same way as RFI. DRFI will be analyzed with the same method as iDFS.

#### 6.4.2.7 Disease-Free Survival

Disease-free survival is defined as the time from randomization to the first occurrence of disease recurrence or death from any cause.

Events defining DFS:

- Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast)
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site—other than the two above mentioned sites—that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
- Contralateral invasive breast cancer
- Ipsilateral or contralateral DCIS
- Second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinoma of any site)
- Death attributable to any cause including breast cancer, non-breast cancer, or unknown cause (but cause of death should be specified if at all possible)

Disease-free survival will be analyzed with the use of the same methodology as specified for iDFS and will follow similar censoring rules.

#### 6.4.2.8 Patient-Reported Outcomes of Role and Physical Function and GHS/HRQoL

The primary PRO endpoints are mean and mean changes from baseline score in function (role, physical) and GHS/HRQoL. Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for the functional (role [Question (Q) 6, Q7], physical [Q1–Q5]) and the GHS/HRQoL (Q29, Q30) scales of the EORTC QLQ-C30 at each assessment timepoint for each arm. The mean (and 95% CI) and median of the absolute scores and the changes from baseline will be reported for interval and continuous variables. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and GHS/HRQoL scales (Osoba et al. 1998; Cocks et al. 2011).

The EORTC QLQ-C30 (Version 3) data will be scored according to the EORTC scoring manual (Fayers et al. 2001). The PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm. Details of the analyses, including methods for handling missing data, are specified in the Statistical Analysis Plan (SAP).

Missing data will be assessed and reported by cycle. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

### 6.4.3 Exploratory Efficacy Endpoints

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

Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for all disease/treatment-related symptom items and scales, and the emotional, social function scales of the EORTC QLQ-C30 (see Appendix 3) at each assessment timepoint for each arm.

#### 6.4.3.2 FACT-G, GP5 Single Item Data

A descriptive analysis of absolute scores and the proportion of patients selecting each response option at each assessment timepoint by treatment arm will be reported for item GP5 (″I am bothered by side effects of treatment″) from the FACT-G physical well-being subscale (see Appendix 4). Item GP5 from version 4 of the FACT-G questionnaire will be scored according to the FACIT scoring manual (Cella 1997).

#### 6.4.3.3 Health Economic EQ-5D-5L Data

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

## 6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

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

Verbatim descriptions of adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately: adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade $\geq 3$ adverse events, adverse events leading to death, serious adverse events, and adverse events of special interest, see Section 5.2.3.

All deaths and causes of death will be summarized.

Relevant laboratory values will be summarized by time, with NCI CTCAE (v5.0) Grade 3 and Grade 4 values identified, where appropriate. Changes in NCI CTCAE grade will be tabulated by treatment arm.

## 6.6 PHARMACOKINETIC ANALYSES

Samples will be collected for PK analysis of atezolizumab serum concentrations in all patients in the atezolizumab-containing arm. Serum concentrations of atezolizumab will be reported as individual values and descriptive statistics will be summarized by treatment arm. Serum concentrations of atezolizumab over time will be plotted as individual and as mean concentrations by treatment arm.

The effect of positive ADA on the serum concentrations of atezolizumab may be explored.

## 6.7 IMMUNOGENICITY ANALYSES

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

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, and pharmacokinetics may be investigated.

## 6.8 BIOMARKER ANALYSES

The primary endpoint (iDFS) will be assessed in the PD-L1 IC1/2/3 population as a secondary endpoint.

Exploratory biomarker analyses will be performed in baseline pretreatment, on-treatment, follow-up and recurrence samples in an effort to understand the association of these markers with study treatment outcome, including efficacy and/or adverse events. The biomarkers may include, but will not be limited to, PD-L1, stromal TILs, and other biomarkers in tumor and blood, as defined by IHC, quantitative reverse transcription PCR, NGS, or other methods.

## 6.9 INTERIM ANALYSES

### 6.9.1 Invasive Disease-Free Survival (Specified)

*In a response to a Health Authority request, a formal interim analysis will be conducted in mid-March 2023 to determine the ability of the study to provide an acceptable benefit-risk assessment upon trial conclusion. This interim analysis will include both assessment of efficacy and futility for iDFS based on the available efficacy (approximately 62% of the total iDFS events) and safety data. To control the Type I error in multiple efficacy analyses of iDFS, the interim and final efficacy analyses boundaries for statistical significance will be determined based on the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary. For the first interim analysis, statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $\leq 0.0088$ (observed HR $\leq 0.71$); a non-binding futility boundary is set at the iDFS hazard ratio of 1, thus futility can be declared if the observed iDFS HR at the first interim analysis is greater than 1.*

*The second* interim efficacy analysis of iDFS will be performed when approximately 80% of the total planned number of iDFS events have occurred. On the basis of the assumption presented in Section 6.1, it is projected that 80% (312) iDFS events will have been observed approximately 59 months after the first patient is randomized.

*For the second interim efficacy analysis* of iDFS, statistical significance will be determined based on the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary. Statistical significance will be declared if the p-value from the two-sided stratified log-rank test $is \leq 0.0218$ (observed HR $\leq 0.77$) depending on the actually observed number of events. If the null hypothesis for iDFS is not rejected at the interim analyses and the study continues, the final analysis of iDFS will be performed when approximately $390\ iDFS\ events$ have occurred; statistical significance will be declared if the p-value from the two-sided stratified log-rank test is $p \leq 0.0422$ (observed HR $\leq 0.81$).

### 6.9.2 Invasive Disease-Free Survival (Optional)

To adapt to information that may emerge during the course of this study, in order to ensure patient benefit, the Sponsor may choose to conduct one additional interim efficacy analysis after at least 80% of the total planned number of iDFS events have occurred for the primary endpoint of iDFS. This will only be conducted after endorsement by the SC. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The interim analysis/analyses will be conducted by an external statistical group and reviewed by the IDMC. The Sponsor will remain blinded to the results. Interactions between the IDMC and Sponsor will be carried out as specified in the IDMC Charter.

The decision to conduct an additional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The IDMC Charter will document potential recommendations the IDMC can make to the SC of the study as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the IDMC Charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets alpha-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will include an assessment of the predictive probability that the specified endpoint will achieve statistical significance.

### 6.10 SUBGROUP ANALYSES

Besides the subgroup analyses of iDFS mentioned in Section 6.4.2 and implicated subgroup analyses mentioned in Section 6.8, to assess the consistency of treatment benefit study results in subgroups defined by demographic and relevant baseline characteristics (including geographical region), iDFS and OS in these subgroups will be evaluated.

## 7. DATA COLLECTION AND MANAGEMENT

### 7.1 DATA QUALITY ASSURANCE

Institut Jules Bordet/Clinical Trials Support Unit (IJB/CTSU), an academic research center affiliated with BIG will be responsible for all data management activities of this study. This will include set-up and build of the EDC system, quality checking of the database throughout study conduct, and study closeout. 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, IJB/CTSU will issue queries to the sites, which the sites will resolve electronically in the EDC system in a timely manner.

IJB/CTSU will produce a Data Management Plan that describes the quality checking to be performed on the data. The EDC data and non-CRF data will be transferred from Frontier Science in SDTMv format to Roche on an agreed frequency using applicable procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of IJB/CTSU's data management plans and specifications. Data as agreed by the Sponsor and IJB/CTSU will be periodically transferred electronically from the IJB/CTSU to the Sponsor, and the applicable procedures will be used to handle and process the electronic transfer of these data.

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

The PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

## 7.2 ELECTRONIC CASE REPORT FORMS

The eCRFs are to be completed through use of IJB/CTSU's Rave EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. The 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. The 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 as Subject PDF reports from the study database, which will be shared via a Secure File Transfer Protocol (SFTP) with the site and must be kept with the study records. Acknowledgement of receipt, download and access to the reports is required.

## 7.3 SOURCE DATA DOCUMENTATION

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

The investigator/institution should maintain adequate and accurate source documents, which should be attributable, legible, contemporaneous, original, accurate, and complete, as referenced in ICH E6 (R2) in Section 8.1.

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, PRO questionnaires, 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 and review, the investigators and institutions must provide the Sponsor/Sponsor Representative/contract research organization (CRO) direct access to applicable source documents and reports for trial-related monitoring, Sponsor/Sponsor Representative/CRO audits, and IRB/Ethics Committee 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, paper PRO data, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. For patients from China, all samples and data will be handled in accordance with the HGRAC requirement and the pertinent HGRAC approval letter for this study. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval. After that period of time, the documents may be destroyed, subject to local regulations.

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

The Sponsor will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 (R2) guideline for GCP and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

## 8.2 INFORMED CONSENT

A study-dedicated ICF (and ancillary sample ICF such as a Child's Informed Assent Form or Mobile 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 ICF, or any alternate consent forms proposed by the site (collectively, the ″Consent Forms″) before IRB/Ethics Committee submission. The final IRB/Ethics Committee-approved Consent Forms must be provided to the Sponsor or designee for health authority submission purposes according to local requirements.

If applicable, the ICF 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 ICFs 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 ICFs 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/Ethics Committee-approved ICFs must be provided to the Sponsor or designee for health authority submission purposes.

Patients must be re-consented to the most current version of the ICF (or to a significant new information/findings addendum in accordance with applicable laws and IRB/Ethics Committee policy) during their participation in the study. For any updated or revised ICFs, 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 ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICF 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 ICF 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 ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/Ethics Committee by the Principal Investigator and reviewed and approved by the IRB/Ethics Committee before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/Ethics Committee.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/Ethics Committee annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/Ethics Committee. Investigators are also responsible for promptly informing the IRB/Ethics Committee of any protocol amendments (see 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/Ethics Committee. 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/Ethics Committee, and archived in the site's study file.

## 8.4 CONFIDENTIALITY

*Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such*

*data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.*

The Sponsor and designees maintain 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 ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective ALEXANDRA/IMpassion030 Publication and Presentation Policy (see Section 9.5).

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/Ethics Committee for each study site, as appropriate.

### 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor or designee with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor or designee 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., last patient, last visit).

## 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, ICF, and documentation of IRB/Ethics Committee 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 according to defined study procedures. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor or designee and to the IRB/Ethics Committee in accordance with established IRB/Ethics Committee 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 QUALITY CONTROL AND QUALITY ASSURANCE

Site visits and quality assurance audits 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/Ethics Committees to inspect facilities and records relevant to this study.

The purpose of a Sponsor audit or Health Authority inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements. The investigator should contact the Sponsor or designee immediately if contacted by a Health Authority about an upcoming inspection.

## 9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored by F. Hoffmann-La Roche Ltd and conducted in collaboration with BIG, AFT, IJB/CTSU and Frontier Science Foundation. Approximately 370–450 sites globally will participate in the study and up to 2300 patients will be randomized. It is estimated that the study will enroll patients over approximately 4 years. Randomization will occur through the IxRS.

Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IDMC will evaluate safety and efficacy data during the study (see Section 3.1.1).

## 9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the SC, the Academic partners, and the Sponsor are dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The SC, the Academic partners, and the Sponsor will comply with all requirements for publication of study results. A trial-specific publication and presentation Policy, namely ALEXANDRA/IMpassion030 Publication and Presentation Policy, developed by the Academic partners and the Sponsor, will be adhered to.

The results of this study will 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 SC, the Academic partners, and the Sponsor aim 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 SC, the Academic partners, and the Sponsor aim to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

All manuscripts and/or abstracts must be provided to BIG headquarters in order to submit to the SC and the Sponsor, for review and comment prior to submission for publication or presentation. The SC approval must be granted prior to any publication.

After the publication of the results of the primary and secondary objectives, (or 12 months after the completion of the study as defined in the protocol), BIG Groups/individual institutions may be allowed to publish/present the data and results from their site(s), provided the following conditions are met:

- The proposed Publication or Presentation is in line with the principles outlined in the ALEXANDRA/IMpassion030 Publication and Presentation Policy and first submitted to the SC for review and comment.
- Prior to submission of a proposed publication or presentation, Roche, as Sponsor of the Study, shall have the right to review and comment on the content of the material to be published or presented. 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.
- The publication or presentation cannot be made in the name of the study but should acknowledge the study as the source of the data used for the publication or presentation, the Academic partners and the Sponsor.

Guidance on the authorship, which must be in line with International Committee of Medical Journal Editors authorship requirements, will be provided in the ALEXANDRA/IMpassion030 publication and Presentation Policy. Any formal publication

or presentation of the study in which contribution of the Academic partners or Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Academic partners or Sponsor personnel.

## 9.6 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB/Ethics Committee 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


Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011;47:8–32.

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

Abe H, Mori T, Kawai Y, et al. Feasibility and toxicity of docetaxel before or after fluorouracil, epirubicin and cyclophosphamide as adjuvant chemotherapy for early breast cancer. Int J Clin Oncol 2013;18:487–91.

Adams S, Diamond JR, Hamilton EP, et al. Abstract 1009: Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC). J Clin Oncol 2016;34(15 Suppl):1009.

Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol 2020;38:1346–66.

Alvarez RH, Bianchini G, Hsu L, et al. Abstract P5-10-02: Clinical outcome of two sequences of administering paclitaxel (P) and anthracyclines (A) as primary systemic therapy (PST) and adjuvant chemotherapy (ACT) in breast cancer (BC) patients: a retrospective analysis from the M. D. Anderson Cancer Center (MDACC). Cancer Res 2010;70 (24 Suppl):P5-10-02.

Anders C, Carey LA. Understanding and treating triple-negative breast cancer. Oncology (Williston Park) 2008;22:1233–43.

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Au HJ, Ringash J, Brundage M, et al. Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG. Expert Rev Pharmacoecon Outcomes Res 2010;10:119–28.

Barrett T, Bowden DJ, Greenberg DC, et al. Radiological staging in breast cancer: which asymptomatic patients to image and how. Brit J Cancer 2009;101:1522–28.

Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006;295:1658–67.

Bines J, Earl H, Buzaid AC, et al. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014;25:1079–85.

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

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

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

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

Budd GT, Barlow WE, Moore HCF, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. J Clin Oncol 2014;33:58–64.

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

Cameron D, Brown J, Dent R, et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol 2013;14:933–42.

Cardoso F, Ferreira Filho AF, Crown J, et al. Doxorubicin followed by docetaxel versus docetaxel followed by doxorubicin in the adjuvant treatment of node positive breast cancer: results of a feasibility study. Anticancer Res 2001;21:789–95.

Cella D. Manual of the functional assessment of chronic illness therapy (FACIT) measurement system version 4. Evanston, IL: Center on Outcomes, Research and Education (CORE) at Evanston Northwestern Healthcare and Northwestern University, 1997.

Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy (FACT) scale: development and validation of the general measure. J Clin Oncol 1993;11:570–9.

Chen DS, Irving BA, Hodi FS, et al. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431–9.

Clemons M, Fergusson D, Simos D, et al. A multi-centre, randomised trial comparing schedules of G-CSF (filgrastim) administration for primary prophylaxis of chemotherapy-induced febrile neutropenia in early stage breast cancer. Ann Oncol 2020;31;951–57.

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

Colleoni M, Gray KP, Gelber S, et al. Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early breast cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34:3400–8.

Crawford J, Caserta C, Roila F, et al., on behalf of the ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO recommendations for the applications. Ann Oncol 2009;20:162–5.

Del Mastro L, De Placido S, Bruzzi P, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet 2015;385:1863–72.

DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Denkert C, Loibl S, Noske A, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2010;28:105–13.

Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007;13:4429–34.

Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–1717.

[EMA] European Medicines Agency. Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man: the use of patient-reported outcome (PRO) measures in oncology studies [resource on the Internet]. April 2016 [cited 11 July 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205159.pdf.

Emens LA, Braiteh FS, Cassier P, et al. Abstract 2859: Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer (TNBC). Cancer Res 2015;75(15 Suppl):2859.

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

Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 scoring manual, 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

[FDA] U.S. Food and Drug Administration. The voice of the patient report: breast cancer [resource on the Internet]. 2 April 2015 [cited 11 July 2017]. Available from: https://www.fda.gov/downloads/Drugs/NewsEvents/UCM464932.pdf

[FDA] U. S. Food and Drug Administration. Structured approach to benefit-risk assessment in drug regulatory decision-making. PDUFA implementation plan: fiscal years 2013–2017 [resource on the Internet]. February 2013 [cited 11 July 2017]. Available from: http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.

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

Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012 v 1.0: IARC CancerBase No. 11 [resource on the internet]. 2013 [cited 11 July 2017]. Available from: http://globocan.iarc.fr/.

Foukakis T, von Minckwitz G, Bengtsson NO, et al. Effect of tailored dose-dense chemotherapy vs standard 3-weekly adjuvant chemotherapy on recurrence-free survival among women with high-risk early breast cancer: a randomized clinical trial. JAMA 2016;316:1888–96.

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

Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–75.

Haffty B, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in consevatively manager triple-negative early-stage breast cancer. J Clin Oncol 2006;10:5652–7.Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976–83.

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

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.

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

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Hoffmann-La Roche. A study of pertuzumab in addition to chemotherapy and trastuzumab as adjuvant therapy in patients with HER2-positive primary breast cancer (APHINITY) [resource on the Internet]. 2011 [updated 20 April 2017; cited 11 July 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT01358877.

Hoffmann-La Roche. A study of trastuzumab emtansine versus trastuzumab as adjuvant therapy in patients with HER2-positive breast cancer who have residual tumor in the breast or axillary lymph nodes following preoperative therapy (KATHERINE) [resource on the Internet]. 2013 [updated 14 June 2017; cited 11 July 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT01772472.

Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review, 1975–2013 [resource on the Internet]. National Cancer Institute. April 2016 [updated 12 September 2016; cited 11 July 2017]. Available from: http://seer.cancer.gov/csr/1975_2013/.

Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 2007;25:2127–32.

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

Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Kassam F, Enright K, Dent R, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer 2009;9:29–33.

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

Lee HJ, Lee JJ, Song IH, et al. Prognostic and predictive value of NanoString-based immune-related gene signatures in a neoadjuvant setting of triple-negative breast cancer: relationship to tumor-infiltrating lymphocytes. Breast Cancer Res Treat 2015;151:619–27.

Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2011;121:2750–67.

Ma CX, Luo J, Ellis MJ. Molecular profiling of triple negative breast cancer. Breast Dis 2011;32:73–84.

Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol 2005;23:3686–96.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Canc Res 2008;27:1–31.

[NCCN] National Comprehensive Cancer Network. NCCN Guidelines®: Breast cancer v2 [resource on the Internet]. 2016 [cited May 2016]. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

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

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

Petersen JA, Gauthier MA, Piault E, et al. Abstract P1-10-20: importance of the patient voice in drug development: early-stage breast cancer and measurement gaps concerning the treatment experience. Cancer Res 2016;76(4 Suppl):P1-10-20.

Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432–44.

Piedbois P, Serin D, Priou F, et al. Dose-dense adjuvant chemotherapy in node-positive breast cancer: docetaxel followed by epirubicin/cyclophosphamide (T/EC), or the reverse sequence (EC/T), every 2 weeks, versus docetaxel, epirubicin and cyclophosphamide (TEC) every 3 weeks. AERO B03 randomized phase II study. Ann Oncol 2007;18:52–7.

Pistelli M, Pagliacci A, Battelli N, et al. Prognostic factors in early-stage triple-negative breast cancer: lessons and limits from clinical practice. Anticancer Res 2013;33:2737–42.

Puhalla S, Mrozek E, Young D, et al. Randomized phase II adjuvant trial of dose-dense docetaxel before or after doxorubicin plus cyclophosphamide in axillary node-positive breast cancer. J Clin Oncol 2008;26:1691–7.

Rosa Mendoza ES, Moreno E, Caguioa PB, et al. Predictors of early distant metastasis in women with breast cancer. J Cancer Res Clin Oncol 2013;139:645–52.

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

Ryerson AB, Miller J, Eheman CR. Reported breast symptoms in the national breast cancer and cervical cancer early detection program. Cancer Causes Control 2015;26:733–40.

Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer 2003;106:416–22.

Schalper KA, Velcheti V, Carvajal D, et al. In situ tumor PD-L1 mRNA expression is associated with increased TILs and better outcome in breast carcinomas. Clin Cancer Res 2014;20:2773–82.

Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2015;26(Suppl 5);v8–30.

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

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006:3187–205.

Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358:1663–71.

Sparano JA, Zhao F, Martino S, et al. Long-term follow-up of the E1199 phase III trial evaluating the role of taxane and schedule in operable breast cancer. J Clin Oncol 2015;33:2353–60.

Tan D, Marchio C, Jones, R, et al. Triple-negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat 2008;111:27–44.

TECENTRIQ® (atezolizumab) injection, Package Insert, Genentech, Inc.

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.

Webster K, Odom L, Peterman A. et al. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: validation of version 4 of the core questionnaire. Quality of Life Research 1999;8:604.

Wildiers H, Dirix L, Neven P et al. Delivery of adjuvant sequential dose-dense FECDoc to patients with breast cancer is feasible, but dose reductions and toxicity are dependent on treatment sequence. Breast Cancer Res Treat 2009;114:103–12.

Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105–22.

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.

# Appendix 1 Schedule of Activities

| | Screening [a] | Treatment [b] | | Treatment Discontinuation [c] ≤30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B) | Follow–Up [d] |
|---|---|---|---|---|---|
| | | Induction (28–day Cycles) (Cycles 1–5; Weeks 1–20) | Arm A: Maintenance Arm B: Monitoring (21–day Cycles) (Cycles 6–16; Weeks 21–53) | | |
| | Days –28 to –1 | Day 1 of each cycle (±3 days) | Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days) | | |
| Informed consent | x [e] | | | | |
| Baseline tumor tissue sample submission for HER2, HR, and PDL1 determination and exploratory biomarkers (mandatory) | x [f] | | | | |
| Demographic data | x | | | | |
| Medical history and baseline conditions | x | | | | |
| Disease status assessments [g] | | x | | | x |
| EORTC QLQ–C30, EQ–5D–5L [h] | | x [h] (±3 days) | Arm A: x [h] (±3 days) Arm B: x [h] (±7 days) | x [h] (±3 days) | x [i] |
| FACT-G, single item GP5 [h] | | x [j] (±3 days) | Arm A: x [j] (±3 days) Arm B: x [h] (±7 days) | x [j] (±3 days) | x [i] |
| Vital signs [k] | x | On each infusion day | Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6) | x | |

**Appendix 1 Schedule of Activities (cont.)**

| | Screening [a] | Treatment [b] | | Treatment Discontinuation [c] ≤30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B) | Follow–Up [d] |
|---|---|---|---|---|---|
| | | Induction (28–day Cycles) (Cycles 1–5; Weeks 1–20) | Arm A: Maintenance Arm B: Monitoring (21–day Cycles) (Cycles 6–16; Weeks 21–53) | | |
| | Days –28 to –1 | Day 1 of each cycle (±3 days) | Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days) | | |
| Weight | x | x | Arm A: Day 1 of each cycle | | |
| Height | x | | | | |
| Complete physical examination [l] | x | | | x | x [g] |
| Limited physical examination [m] | | x | Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6) | | |
| ECOG Performance Status | x | | | x | |
| ECG (12-lead) [n] | x | As clinically indicated | | | |
| ECHO/MUGA scan [o] | x [o] (±28 days) | x [o] | x [o] (±14 days) | x [o] | x [o] (±28 days) |

**Appendix 1 Schedule of Activities (cont.)**

| | Screening [a] | Treatment [b] | | Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B) | Follow–Up [d] |
|---|---|---|---|---|---|
| | | Induction (28–day Cycles) (Cycles 1–5; Weeks 1–20) | Arm A: Maintenance Arm B: Monitoring (21–day Cycles) (Cycles 6–16; Weeks 21–53) | | |
| | Days −28 to −1 | Day 1 of each cycle (±3 days) | Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days) | | |
| Hematology [p] | x | On each infusion day | Arm A: Day 1 of each cycle<br>Arm B: Day 1 of every other cycle (starting with Cycle 6) | x | |
| Chemistry [q] | x | On each infusion day | Arm A: Day 1 of each cycle<br>Arm B: Day 1 of every other cycle (starting with Cycle 6) | x | |
| Menopausal status | x | | | x | 1 year after treatment discontinuation at closest visit |
| Pregnancy test [r] | x [s] | x [r] | x [r] | x [r] | x [r] |
| Coagulation (INR, aPTT) | x | | | x | |
| TSH, free T3 (or total T3 [t]), free T4 | x | x [t] | | x | |
| Viral serology [u] | x | | | | |

**Appendix 1 Schedule of Activities (cont.)**

| | Screening [a] | Treatment [b] | | Treatment Discontinuation [c] ≤30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B) | Follow–Up [d] |
|---|---|---|---|---|---|
| | | Induction (28–day Cycles) (Cycles 1–5; Weeks 1–20) | Arm A: Maintenance Arm B: Monitoring (21–day Cycles) (Cycles 6–16; Weeks 21–53) | | |
| | Days −28 to −1 | Day 1 of each cycle (±3 days) | Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days) | | |
| Urinalysis [v] | x | x [w] | | | |
| Serum autoantibody sample | | See Appendix 2 for detailed schedule. | | | |
| Serum PK sample for atezolizumab | | See Appendix 2 for detailed schedule (Arm A only). | | | |
| Serum ADA sample for atezolizumab | | See Appendix 2 for detailed schedule (Arm A only). | | | |
| Plasma samples for biomarkers | | See Appendix 2 for detailed schedule. | | | |
| Blood sample for RPBS (optional) [x] | | x | | | |
| Radiographic assessments (e.g., CT, MRI, PET) | x [y,z] | As clinically indicated | | | |
| Bilateral mammogram/breast MRI | x [y] | | x [aa] | | x [aa] |
| Tumor biopsy/tumor tissue at relapse, if clinically feasible | | At time of recurrence [bb] | | | |
| Concomitant medications [ii] | x [cc] | x | Arm A: Day 1 of each cycle Arm B: Day 1 of every other cycle (starting with Cycle 6) | x | x [dd] |

**Appendix 1 Schedule of Activities (cont.)**

| | Screening [a] | Treatment [b] | | Treatment Discontinuation [c] ≤ 30 days after Last Dose (Arm A) or Last Monitoring Visit (Arm B) | Follow–Up [d] |
|---|---|---|---|---|---|
| | | Induction (28–day Cycles) (Cycles 1–5; Weeks 1–20) | Arm A: Maintenance Arm B: Monitoring (21–day Cycles) (Cycles 6–16; Weeks 21–53) | | |
| | Days −28 to −1 | Day 1 of each cycle (±3 days) | Arm A: Day 1 of each cycle (±3 days); Arm B: Day 1 of every other cycle (±7 days) | | |
| Adverse events [ee] | x [ee] | x [ee] | Arm A: Day 1 of each cycle<br>Arm B: Day 1 of every other cycle (starting with Cycle 6) | x | x [ee] |
| Study treatment administration [ff] | | x[ff] (±1 day for weekly paclitaxel) | x [gg] | | |
| Survival follow-up and anti-cancer treatment | | | | | x [d,hh] |

AC = dose-dense doxorubicin + cyclophosphamide; AC/EC = dose-dense doxorubicin/epirubicin + cyclophosphamide; ADA = anti-drug antibody; CT = computed tomography; EC = dose-dense epirubicin + cyclophosphamide; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQoL 5 Dimension, 5 Level; FACT-G = Functional Assessment of Cancer Therapy–General; FFPE = formalin-fixed paraffin embedded; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hormone receptor; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography; PK = pharmacokinetic; RPBS = Research Project Biological Samples; Q2W = every 2 weeks; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

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

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

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

[b] In the event of treatment delay, study visits should continue as scheduled, if feasible. Patients (both in Arm A and on Arm B) who discontinue study treatment prematurely due to an adverse event should conduct a treatment discontinuation visit and move to the follow-up. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported, including during the follow-up period. Additional tests can be performed, if needed, according to standard medical practice.

[c] Patients will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment (Arm A) or within 30 days after the last monitoring visit (Arm B).

[d] The follow-up period begins from the date of treatment phase completion/early termination visit with a duration of up to 7 years from the date of randomization of the first patient. Visit windows are ±28 days for quarterly, semiannual, and annual assessments.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] After signing of the Informed Consent Form, submission of tumor tissue sample to central laboratory can occur. Tumor tissue, which can be obtained outside the 28-day screening period, should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). An FFPE block or approximately 25 unstained slides (minimum of 20 slides) should be provided from the surgical resection specimen. Biomarker samples should not be collected for patients enrolling from China prior to the approval from Human Genetic Resources Administration of China.

[g] Disease status based on all available clinical assessments should be documented from the date of randomization at the following timepoints (± 28 days): every 3 months during study treatment and up to 3 years, every 6 months from 3 to 5 years, and annually thereafter unless a recurrence as defined in Section 4.6.6 has occurred. In addition to physical examinations and mammograms, liver function tests, bone scans, chest X-rays/diagnostic CT, liver imaging, or other radiographic modality may be considered when clinically indicated to exclude metastatic disease and within a timeline as per current local standard of practice. Disease recurrence must be confirmed pathologically if clinically feasible. In cases of disease recurrence diagnosed at any time during the study, patients will be out of the study schedule and will be followed once a year (starting 1 year after first relapse) until end of study for survival, anti-cancer medications, and new relapse events.

[h] All PRO assessments (EORTC QLQ-C30, followed by the FACT-G single item GP5, and then the EQ-5D-5L questionnaires) must be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory results or health record, before administration of study treatment, and/or prior to the performance of any other study assessments that could bias patients' responses. Interview assessment by a member of the clinical staff will be allowed if the patient is not able to complete the measure on her or his own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be completed by patients at baseline (Cycle 1, Day 1) (±3 days); on Cycle 4, Day 1 (±3 days); on Day 1 of every other cycle thereafter until Cycle 16 (Arm A [± 3 days], Arm B [± 7days]); and at the end of treatment/monitoring visit. In case the treatment is interrupted/delayed, the patient should repeat the PRO assessment at the next visit, corresponding to the treatment administration day.

[i] Patients who discontinue the study treatment phase (eg., Arm A Maintenance and Arm B Monitoring) for any reason will continue to complete the EORTC QLQ-C30, FACT-G single item GP5, and EQ-5D-5L questionnaires in-clinic during the follow-up period at the following timepoints: every 3 months (±28 days) for the first year, every 6 months (±28 days) for Years 2–3, and then annually (±28 days) thereafter.

[j] While on study treatment, all patients will complete the FACT-G, single item GP5 beginning on Cycle 4, Day 1 (±3 days); at Day 1 of every other cycle thereafter until Cycle 16 (Arm A [± 3 days], Arm B [± 7days]); and at the end of treatment/monitoring visit. In case the treatment is interrupted/delayed, the patient should repeat the PRO assessment at the next visit, corresponding to the treatment administration day.

[k] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record vital signs at baseline in the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[l] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Special attention should be paid to cardiovascular symptoms (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs). Record abnormalities observed at baseline in the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Special attention should be paid to cardiovascular symptoms (e.g., abnormally low or irregular pulse, chest pain, tachycardia, swollen legs). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[n] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes or as per local practice prior to ECG recording.

[o] Cardiac monitoring (ECHO/MUGA scans) will be performed in all patients enrolled in the study. ECHO is the preferred method. The same method used for a given patient at screening should be used throughout the study.

For both Arms A and B, ECHO/MUGA scans should be obtained at baseline (i.e., screening ECHO/MUGA), between the second dose of AC/EC and the third dose of AC/EC (which should usually occur approximately between Week 16 and Week 18 if no treatment delays), and then every 3 months [i.e., at Week 26 (± 14 days), at Week 39 (± 14 days), and at Week 52 (± 14 days) if no treatment delays]. ECHO/MUGA scans should be obtained at the early termination visit if not performed within the previous 6 weeks. During the survival follow-up period, ECHO/MUGA scans should be obtained annually until the end of study.

During the follow-up period, ECHO/MUGA scans should be obtained annually until the end of study (except for patients who experienced a recurrence of disease).

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

[q] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH. Magnesium and phosphorus should be included at screening and as clinically indicated during study treatment. Lipase and amylase levels should be determined if clinically indicated by the presence of abdominal symptoms (e.g., abdominal pain, digestive disorders) suggestive of pancreatitis. Bicarbonate/total CO2 should be determined if clinically indicated or considered standard of care.

[r] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at the following specified subsequent visits for women of childbearing potential (including premenopausal women who have had tubal ligation) and women not meeting the definition of postmenopausal: For Arm A at Day 1 of Cycles 1–16, at treatment discontinuation visit, and every 4 weeks until 6 months after treatment discontinuation (last administered dose of study treatment) including for patients who experienced a disease recurrence. For Arm B at Day 1 of Cycles 1–5, at treatment discontinuation visit, and every 4 weeks until 6 months after last administered dose of study treatment including for patients who experienced a disease recurrence. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[s] Screening pregnancy test results must be obtained within 14 days prior to initiation of study treatment.

[t] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter. Patients in Arm B can have thyroid function tests at Cycle 1, Cycle 4, and Cycle 8 and then continue being tested every fourth cycle.

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

[v] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[w] Urinalysis should be performed as clinically indicated during study treatment.

[x] Not applicable for a site that has not been granted approval for RPBS. Performed only for patients at participating sites who have provided written informed consent to participate. Whole blood for DNA isolation will be collected from patients who have consented to optional RPBS at Week 1, Day 1 (Cycle 1, Day 1). If, however, the RPBS genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[y] Within 6 months prior to randomization (except for patients who do not have any remaining breast tissue due to prior prophylactic breast surgery).

[z] Per local standard practice

[aa] Mammograms of any remaining tissue should be performed at least annually (±3 months) from the date of the mammogram performed at screening/surgery and as clinically indicated based on findings from physical examinations.

[bb] Patients are required to undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease relapse. Examples of when tumor biopsy sample collection may be considered not clinically feasible include, but are not limited to, cases where the location of the tumor renders tumor biopsy unsafe or not clinically feasible per the investigator due to patient concerns or is prohibited by the institution or country. Biomarker samples should not be collected for patients enrolling from China prior to the approval from Human Genetic Resources Administration of China.Biopsies should be performed within 40 days after recurrence. An FFPE block or at least 20 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, bone metastases, and lavage samples are not acceptable. For core needle biopsy specimens, at least two cores should be submitted for evaluation. See Section 4.6.7 for tissue sample requirements.

[cc] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit. Record all prior anti-cancer therapies.

[dd] All new anti-cancer treatments are to be reported during the follow-up period.

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

[ff] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Paclitaxel should be administered as an IV infusion QW (7 [± 1] days). During the induction treatment phase, the interval between the end of the weekly paclitaxel (Cycle 3 Visit 4) and the initiation of AC or EC Q2W (Cycle 4 Visit 1) should be 7 days (± 1 day), (i.e., Cycle 4 Visit 1 should be performed at maximum 8 days from Cycle 3 Visit 4, as shown in the study schema [see Figure 1 of the Protocol]). Cyclophosphamide and doxorubicin/epirubicin will be administered Q2W (14 [± 3] days). The 14-days interval only starts after Cycle 4 Visit 1 and the respective ± 3 days window allowed per protocol is only applicable from Cycle 4 Visit 2.

[gg] Study drug administration during the maintenance phase for the atezolizumab-containing arm only

[hh] Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits (unless the patient withdraws consent, or the study is terminated). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only (if allowed per country regulation). Every effort should be made to obtain information on patients who withdraw from the study treatment and/or assessments but have agreed to be contacted for further information (i.e., partial withdrawal). Partial withdrawal from the study, with consent to allow collection of information regarding disease recurrence, survival status, and reportable toxicity should be documented in both the medical records and in the eCRF (i.e., the patient accepted to be contacted for collection of these data despite she/he withdrew consent from the study treatment and/or procedures).

[ii] For patients in Arm B (Monitoring), only medications given for reportable adverse events as per protocol (see Section 5.3.1) as well as new anti-cancer treatments should be collected.

# Appendix 2 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

| Visit | Time | Sample |
|---|---|---|
| Screening/Baseline | NA | • FFPE tumor tissue from surgical resection (block or 25 slides) [c] |
| Day 1 of Week 1 (Cycle 1) | Prior to the first dose | • Atezolizumab PK (serum) [a, b]<br>• Atezolizumab ADA (serum) [a, b]<br>• Biomarker (plasma) [c]<br>• Serum autoantibody sample<br>• Optional RPBS (whole blood) |
| | 30 min (±10 min) following atezolizumab infusion | • Atezolizumab PK (serum) [a, b] |
| Day 1 of Week 21 (±3 days) | Pre-dose | • Biomarkers (plasma) [c] |
| Day 1 of Weeks 5, 9, 13, 21, 33, and 45 (Cycles 2, 3, 4, 6, 10, and 14) | Pre-dose | • Atezolizumab PK (serum) [a, b]<br>• Atezolizumab ADA (serum) [a, b] |
| Treatment discontinuation visit (≤30 days after last dose) | NA | • Atezolizumab PK (serum) [a, b]<br>• Atezolizumab ADA (serum) [a, b] |
| Day 1 of Week 52 (±1 week) | | • Biomarkers (plasma) [c] |
| 18 months post initial treatment (±28 days) | NA | • Biomarkers (plasma) [c] |
| 24 months post initial treatment (±28 days) | NA | • Biomarkers (plasma) [c] |
| 36 months post initial treatment (±28 days) | NA | • Biomarkers (plasma) [c] |
| At disease recurrence | NA | • FFPE tumor tissue (block or 20 slides) [c]<br>• Biomarkers (plasma) [c] |
| At time of possible immune-related toxicity | NA | • Serum autoantibody sample |

ADA = anti-drug antibody; FFPE = formalin-fixed, paraffin embedded; HGRAC = Human Genetic Resources Administration of China; NA = not applicable; PK = pharmacokinetic; RPBS = Research Project Biological Samples.

Note: Unless otherwise described above, all other study visits and assessments in Appendix 2 should be performed within ±1 week of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] Atezolizumab PK and ADA samples are to be taken only in patients receiving atezolizumab (Arm A).

[b] Patients enrolling from China are exempt from providing atezolizumab PK (serum) and atezolizumab ADA (serum) during the study.

[c] Biomarker samples (blood, tissue) should not be collected for patients enrolling from China prior to the approval from HGRAC. Samples collected should match the number of slides or volume of samples allowed per HGRAC approval.

# Appendix 3 European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30

**Do not reproduce or distribute**. The Sponsor will provide sites with all instruments to be completed in this study.

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

## Appendix 3 European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (cont.)

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 4 FACT-G Single-Item GP5

**Do not reproduce or distribute**. The Sponsor will provide sites with all instruments to be completed in this study.

**GP5 (Version 4)**

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP5 | I am bothered by side effects of treatment..... | 0 | 1 | 2 | 3 | 4 |

# Appendix 5 EQ-5D-5L


**Health Questionnaire**

**English version for the UK**

**Do not reproduce or distribute**. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please check the ONE box that best describes your health TODAY.

**MOBILITY**

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

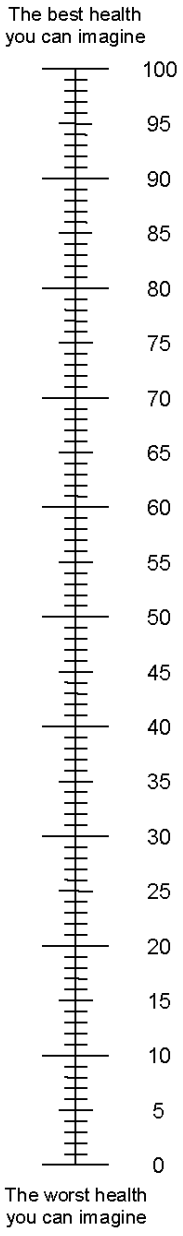
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



# Appendix 6 Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise as needed in case of any uncertainty over autoimmune exclusions.

## AUTOIMMUNE DISEASES AND IMMUNE DEFICIENCIES

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

# Appendix 7 Anaphylaxis Precautions

## EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

## PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations

# Appendix 8 Radiotherapy Guidelines

Radiotherapy can only be administered after chemotherapy is complete. Treatment with atezolizumab during adjuvant radiotherapy is permitted.

## I. BREAST-CONSERVING THERAPY

### MANDATORY: BREAST RADIOTHERAPY (RT) AFTER COMPLETE LOCAL EXCISION

Breast RT may be contraindicated in patients with significant comorbidity (e.g., scleroderma and systemic lupus erythematous). Reasons for not delivering breast RT after complete local excision of the primary breast cancer should be documented in the electronic Case Report Form.

### Target Volume

- Whole breast including the primary tumor bed
- Primary tumor bed boost in conjunction with whole breast RT may be used as per local policy declared by the center prior to local activation.
- Partial breast RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: See Item III below.

### Dose Fractionation

- Whole breast—recommended schedules:
  a) 50 Gy in 25 fractions, 5 fractions per week; or
  b) 42.5 Gy in 16 fractions, 5 fractions per week; or
  c) 40 Gy in 15 fractions, 5 fractions per week.

Other schedules may be used as per local policy declared by the center prior to local activation.

- Primary tumor bed boost in conjunction with whole breast RT: As per local policy declared by the center prior to local activation.
- Partial breast RT: As per local policy declared by the center prior to local activation.

### Treatment Planning

- Computer tomography (CT)-based treatment planning is strongly recommended for whole breast RT and tumor bed boost.
- CT-based treatment planning is mandatory for partial breast irradiation delivered using external beam RT.

## II. POST-MASTECTOMY RADIOTHERAPY

### MANDATORY:

a) 4 or more positive axillary nodes or

b) "Non-resectable" microscopic positive deep margin (invasive carcinoma or ductal carcinoma in situ)

### OPTIONAL:

a) 1–3 positive axillary nodes after axillary dissection

b) Higher risk node-negative disease (e.g., T3 primary in the presence of high histologic grade and/or lymphovascular invasion)

### Target Volume

- Whole chest wall
- Primary tumor bed boost in conjunction with chest wall RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: See Item III below.

### Dose Fractionation

- Whole chest wall: Recommended schedule is 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation.
- Primary tumor bed boost in conjunction with chest wall RT: As per local policy declared by the center prior to local activation.

### Treatment Planning

- CT-based treatment planning is strongly recommended for chest wall RT.

## III. REGIONAL NODAL RADIOTHERAPY

For patients who have completed sentinel lymph node biopsy alone or axillary lymph node dissection as per protocol:

### RECOMMENDED:

Any breast surgery, 4 or more positive axillary nodes

1–2 positive axillary lymph nodes after mastectomy plus SLNB and no axillary dissection performed

### OPTIONAL:

Any breast surgery, 1–3 positive axillary nodes

## Target Volume

- Required:
  a) Supraclavicular fossa if there are 4 or more positive axillary nodes;
  b) Internal mammary nodes if tumor involvement is clinically or pathologically confirmed.
- Optional:
  a) Supraclavicular fossa if there are 1–3 positive axillary nodes;
  b) Axilla as per local policy declared by the center prior to local activation (e.g., known or high risk of residual axillary disease post-surgery);
  c) Internal mammary nodes if there is a high risk of tumor involvement as per local policy declared by the center prior to local activation.

## Dose Fractionation

- Recommended schedule: 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation. Hypofractionated schedules are not recommended.

## Treatment Planning

- CT-based treatment planning is strongly recommended for supraclavicular fossa and/or axillary RT.
- CT-based treatment planning is mandatory for internal mammary nodal RT.

# Appendix 9 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

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. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

*The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.*

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.*

The investigator should consider the benefit-risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

## DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study.

## TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after the event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

## MANAGEMENT GUIDELINES

### PULMONARY EVENTS

*Pulmonary events may present as new or worsening* cough, *chest pain, fever,* dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 1.

## Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

| Event | Management |
|---|---|
| Pulmonary event, Grade 1 | • Continue atezolizumab and monitor closely.<br>• Re-evaluate on serial imaging.<br>• Consider patient referral to pulmonary specialist.<br>• For Grade 1 pneumonitis, consider withholding atezolizumab. |
| Pulmonary event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c, d]<br>• For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event. |
| Pulmonary event, Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c, d]<br>• *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.*<br>• Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. The Medical Monitor is available to advise as needed.

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

## HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

### Table 2 Management Guidelines for Hepatic Events

| Event | Management |
|---|---|
| Hepatic event, Grade 1 | • Continue atezolizumab.<br>• Monitor LFTs until values resolve to within normal limits. |
| Hepatic event, Grade 2 | **All events:**<br>• Monitor LFTs more frequently until return to baseline values.<br>**Events of > 5 days' duration:**<br>• Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Hepatic event, Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

## GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

### Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

| Event | Management |
|---|---|
| Diarrhea or colitis, Grade 1 | • Continue atezolizumab.<br>• Initiate symptomatic treatment.<br>• Endoscopy is recommended if symptoms persist for >7 days.<br>• Monitor closely. |
| Diarrhea or colitis, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Initiate symptomatic treatment.<br>• *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.*<br>• Patient referral to GI specialist is recommended.<br>• For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. *If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.*<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |

## Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

| Event | Management |
|---|---|
| Diarrhea or colitis, Grade 3 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.*<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Diarrhea or colitis, Grade 4 | • Permanently discontinue atezolizumab and contact Medical Monitor. [c]<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

## ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

### Table 4 Management Guidelines for Endocrine Events

| Event | • Management |
|---|---|
| *Grade 1* hypothyroidism | • Continue atezolizumab.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH closely. |
| *Grade 2 hypothyroidism* | • *Consider withholding atezolizumab.*<br>• *Initiate treatment with thyroid replacement hormone.*<br>• *Monitor TSH closely.*<br>• *Consider patient referral to endocrinologist.*<br>• *Resume atezolizumab when symptoms are controlled and thyroid function is improving.* |
| *Grade 3 and 4* hypothyroidism | • Withhold atezolizumab.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH closely.<br>• Refer to an endocrinologist.<br>• *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).*<br>• Resume atezolizumab when symptoms are controlled, and thyroid function is improving.<br>• *Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c] |
| *Grade 1* hyperthyroidism | TSH ≥ 0.1 mU/L and < 0.5 mU/L:<br>• Continue atezolizumab.<br>• Monitor TSH every 4 weeks.<br>• Consider patient referral to endocrinologist.<br>TSH < 0.1 mU/L:<br>• Follow guidelines for *Grade 2* hyperthyroidism.<br>• Consider patient referral to endocrinologist. |

## Table 4 Management Guidelines for Endocrine Events (cont.)

| Event | • Management |
|---|---|
| *Grade 2 hyperthyroidism* | • *Consider withholding atezolizumab.*<br>• *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.*<br>• *Consider patient referral to endocrinologist.*<br>• *Resume atezolizumab when symptoms are controlled and thyroid function is improving.* |
| *Grade 3 and 4* hyperthyroidism | • Withhold atezolizumab.<br>• Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed.<br>• Refer to endocrinologist.<br>• Resume atezolizumab when symptoms are controlled, and thyroid function is improving.<br>• Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c] |
| Symptomatic adrenal insufficiency, Grade 2–4 | • Withhold atezolizumab for up to 12 weeks after event onset. a<br>• Refer patient to endocrinologist.<br>• Perform appropriate imaging.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Hyperglycemia, Grade 1 or 2 | • Continue atezolizumab.<br>• Initiate treatment with insulin if needed.<br>• Monitor for glucose control. |
| Hyperglycemia, Grade 3 or 4 | • Withhold atezolizumab.<br>• Initiate treatment with insulin.<br>• Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.<br>• Monitor for glucose control.<br>• Resume atezolizumab when symptoms resolve, and glucose levels are stable. |

## Table 4 Management Guidelines for Endocrine Events (cont.)

| Event | • Management |
|---|---|
| Hypophysitis (pan-hypopituitarism), Grade 2 or 3 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• Initiate hormone replacement if clinically indicated.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• For recurrent hypophysitis, treat as a Grade 4 event. |
| *Hypophysitis (pan-hypopituitarism), Grade 4* | • *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]<br>• *Refer patient to endocrinologist.*<br>• *Perform brain MRI (pituitary protocol).*<br>• *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.*<br>• *Initiate hormone replacement if clinically indicated.* |

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed

## OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

### Table 5 Management Guidelines for Ocular Events

| Event | Management |
|---|---|
| Ocular event, Grade 1 | • Continue atezolizumab.<br>• Patient referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If symptoms persist, treat as a Grade 2 event. |
| Ocular event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Patient referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Ocular event, Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• Refer patient to ophthalmologist.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed

## *IMMUNE-MEDIATED CARDIAC EVENTS*

*Management guidelines for cardiac events are provided in Table 6.*

## IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis *or associated with pericarditis (see section on pericardial disorders below)* and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted.
An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

### *Immune-Mediated Pericardial Disorders*

*Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).*

*Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.*

*Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.*

*All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.*

*Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.*

## Table 6 Management Guidelines for Immune-Mediated *Cardiac Events*

| Event | Management |
|---|---|
| Immune-mediated myocarditis, Grades 2–4<br><br>*Immune-mediated pericardial disorders, Grades 2–4* | • Permanently discontinue atezolizumab and contact the Medical Monitor.<br>• Refer patient to cardiologist.<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, *or pericardiocentesis* as appropriate.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

## INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

Cytokine-release syndrome is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table 7.

Severe SARS-CoV-2 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 is confirmed, the disease should be managed as per local or institutional guidelines.

## Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome

| Event | Management |
|---|---|
| Grade 1 [a]<br>Fever [b] with or without constitutional symptoms | • Immediately interrupt infusion.<br>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.<br>• If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.<br>• If symptoms recur, discontinue infusion of this dose.<br>• Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration.<br>• In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.<br>• For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. |
| Grade 2 [a]<br>fever [b] with hypotension not requiring vasopressors<br>**and/or**<br>hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by | • Immediately interrupt infusion.<br>• Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.<br>• If symptoms recur, discontinue infusion of this dose.<br>• Administer symptomatic treatment. [c]<br>• For hypotension, administer IV fluid bolus as needed.<br>• Monitor cardiopulmonary and other organ functions closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.<br>• Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy. [e]<br>• Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor.<br>• If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.<br>• For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS.<br>• If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor. |

## Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

| Event | Management |
|---|---|
| Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask | • Permanently discontinue atezolizumab and contact the Medical Monitor. [e]<br>• Administer symptomatic treatment. [c]<br>• For hypotension, administer IV fluid bolus and vasopressor as needed.<br>• Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.<br>• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy. [e]<br>• Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor. |
| Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation) | • Permanently discontinue atezolizumab and contact the Medical Monitor. [e]<br>• Administer symptomatic treatment. [c]<br>• Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.<br>• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.<br>• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).<br>• Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.<br>• Hospitalize patient until complete resolution of symptoms. |

## Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction, MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (v5.0) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature $\geq 38°C$ not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at $\leq 6$ L/min, and high flow is defined as oxygen delivered at $> 6$ L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

[f] Refer to Riegler et al. (2019).

## PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

### Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

| Event | Management |
|---|---|
| Amylase and/or lipase elevation, Grade 2 | **Amylase and/or lipase > 1.5–2.0 × ULN:**<br>• Continue atezolizumab.<br>• Monitor amylase and lipase weekly.<br>• For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.<br>**Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:**<br>• Treat as a Grade 3 event. |
| Amylase and/or lipase elevation, Grade 3 or 4 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to GI specialist.<br>• Monitor amylase and lipase every other day.<br>• If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Immune-mediated pancreatitis, Grade 2 or 3 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to GI specialist.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |

## Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

| Event | Management |
|---|---|
| Immune-mediated pancreatitis, Grade 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• Refer patient to GI specialist.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available as needed.

## DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

### Table 9 Management Guidelines for Dermatologic Events

| Event | Management |
|---|---|
| Dermatologic event, Grade 1 | • Continue atezolizumab.<br>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines). |
| Dermatologic event, Grade 2 | • Continue atezolizumab.<br>• Consider patient referral to dermatologist for evaluation and, if indicated, biopsy.<br>• Initiate treatment with topical corticosteroids.<br>• Consider treatment with higher-potency topical corticosteroids if event does not improve.<br>• If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day. |
| Dermatologic event, Grade 3 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to dermatologist for evaluation and, if indicated, biopsy.<br>• Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Dermatologic event, Grade 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade) | Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:<br>• Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.<br>• Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.<br>• Follow the applicable treatment and management guidelines above.<br>• If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab. |

[a] Atezolizumab may be withheld for a longer period of time (i.e., $>12$ weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to $\leq 10$ mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available as needed.

[b] If corticosteroids have been initiated, they must be tapered over $\geq 1$ month to $\leq 10$ mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

## NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10, *with specific guidelines for myelitis provided in Table 11.*

### Table 10 Management Guidelines for Neurologic Disorders

| Event | Management |
|---|---|
| Immune-mediated neuropathy, Grade 1 | • Continue atezolizumab.<br>• Investigate etiology.<br>• *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.* |
| Immune-mediated neuropathy, *including facial paresis,* Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Investigate etiology and refer patient to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• *For general immune-mediated neuropathy:*<br>– If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>– If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• *For facial paresis:*<br>– *If event resolves fully, resume atezolizumab* [b]<br>– *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact theMedicalMonitor.* [c] |
| Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• Refer patient to neurologist.<br>• Initiate treatment as per institutional guidelines. |
| Myasthenia gravis and Guillain-Barré syndrome (any grade) | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• Refer patient to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent. |

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

## *Table 11 Management Guidelines for Immune-Mediated Myelitis*

| *Event* | *Management* |
|---|---|
| *Immune-mediated myelitis, Grade 1* | • *Continue atezolizumab unless symptoms worsen or do not improve.*<br>• *Investigate etiology and refer patient to a neurologist.* |
| *Immune-mediated myelitis, Grade 2* | • *Permanently discontinue atezolizumab and contact the Medical Monitor.*<br>• *Investigate etiology and refer patient to a neurologist.*<br>• *Rule out infection.*<br>• *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.* |
| *Immune-mediated myelitis, Grade 3 or 4* | • *Permanently discontinue atezolizumab and contact the Medical Monitor.*<br>• *Refer patient to a neurologist.*<br>• *Initiate treatment as per institutional guidelines.* |

## IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

### Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

| Event | Management |
|---|---|
| Immune-mediated meningoencephalitis, all grades | • Permanently discontinue atezolizumab and contact the Medical Monitor.<br>• Refer patient to neurologist.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

## RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

### Table 13 Management Guidelines for Renal Events

| Event | Management |
|---|---|
| Renal event, Grade 1 | • Continue atezolizumab.<br>• Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values. |
| Renal event, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset. [a]<br>• Refer patient to renal specialist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |
| Renal event, Grade 3 or 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor.<br>• Refer patient to renal specialist and consider renal biopsy.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

## IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

### Table 14 Management Guidelines for Immune-Mediated Myositis

| Event | Management |
|---|---|
| Immune-mediated myositis, Grade 1 | • Continue atezolizumab.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines. |
| Immune-mediated myositis, Grade 2 | • Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] |

## Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

| Event | Management |
|---|---|
| Immune-mediated myositis, Grade 3 | • Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c] |
| Immune-mediated myositis, Grade 4 | • Permanently discontinue atezolizumab and contact the Medical Monitor. [c]<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

## HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq 38.5°C$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $< 90$ g/L (9 g/dL) ($< 100$ g/L [10 g/dL] for infants $< 4$ weeks old)
  - Platelet count $< 100 \times 109$/L (100,000/$\mu$L)
  - ANC $< 1.0 \times 109$/L (1000/$\mu$L)
- Fasting triglycerides $> 2.992$ mmol/L (265 mg/dL) and/or fibrinogen $< 1.5$ g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $> 500$ mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated $\geq 2$ standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $> 684$ mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 109$/L (181,000/$\mu$L)
  - AST $\geq 48$ U/L
  - Triglycerides $> 1.761$ mmol/L (156 mg/dL)
  - Fibrinogen $\leq 3.6$ g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 15.

## Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

| Event | Management |
|---|---|
| Suspected HLH or MAS | • Permanently discontinue atezolizumab and contact the Medical Monitor.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy.<br>• If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019)<br>• If event resolves to Grade 1 or better, taper corticosteroids over $\geq$ 1 month. |

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

## REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

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

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology

International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Signature Page for Protocol - WO39391 - TECENTRIQ - v9 - Global/Core - Published
System identifier: RIM-CLIN-470731

| | |
|---|---|
| Approval Task | [redacted]<br>Company Signatory<br>01-Mar-2023 21:01:20 GMT+0000 |