Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial To Evaluate the Efficacy and Safety Of Atezolizumab or Placebo in Combination With Neoadjuvant Doxorubicin + Cyclophosphamide Followed By Paclitaxel + Trastuzumab + Pertuzumab In Early Her2-Positive Breast Cancer

NCT Number: NCT03726879

Document Date: Protocol Version 6: 23-February-2023

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH NEOADJUVANT DOXORUBICIN+CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL+TRASTUZUMAB+PERTUZUMAB IN EARLY HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	BO40747
VERSION NUMBER:	6
EUDRACT NUMBER:	2018-001881-40
NCT NUMBER:	NCT03726879
IND NUMBER:	123277
TEST PRODUCT:	Atezolizumab (RO5541267), Pertuzumab (RO4368451), Trastuzumab (RO0452317), Trastuzumab emtansine (RO5304020)
SPONSOR:	F. Hoffmann-La Roche Ltd
***APPROVAL*:**	See electronic *signature and* date stamp *on the final page of this document*.

CONFIDENTIAL

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
6	See electronic date stamp on the final page of this document
5	12 February 2021
4	14 February 2020
3	4 June 2019
2	22 March 2019
1	9 July 2018

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol BO40747 has been amended to update safety information and align with the Trastuzumab Emtansine Investigator's Brochure, Version 16 and Atezolizumab Investigator's Brochure, Version19.

Additional changes to the protocol are summarized below:

- The synopsis has been simplified to align with European Union Clinical Trial Regulation (Reg. No. 536/2014) and other guidelines.
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 4.1.1, 4.1.2, 4.4.2.2, 4.5.8, 4.5.9, 5.1.10, Appendix 11, and Appendix 12).
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Section 4.1.2 and Appendix 9).
- A new section of cautionary therapies has been added to indicate that certain therapies used to treat chemotherapy-induced thrombocytopenia should be avoided in patients in this study (e.g., thrombopoietin receptor agonists, recombinant thrombopoietins, recombinant interleukin) to align with the Trastuzumab Emtansine Investigator's Brochure, Version 16 (Section 4.4.2.4).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.14.6).
- In alignment with the Trastuzumab Emtansine Investigator's Brochure, Version 16, human recombinant thrombopoeitin has been identified as a risk factor for prolonged thrombocytopenia in patients who are being treated with trastuzumab emtansine (Section 5.1.6.5).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- Language has been added to permit the collection of infant health information if a female patient or a female partner of a male patient becomes pregnant to align with the Trastuzumab Emtansine Risk Management Plan (Sections 5.4.3.1 and 5.4.3.2).
- It has been clarified that there is no requirement to report special situations within 24 hours unless there is a serious adverse event associated with the special situation, in which case the serious adverse event must be reported within 24 hours (Section 5.4.4).
- The Sponsor record retention policy has been clarified (Section 7.1).
- 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).

- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- The medical term “primary biliary cirrhosis” has been replaced by the term “primary biliary cholangitis” to align with the updated preferred term in MedDRA (Appendix 9).
- To align with the Atezolizumab Investigator’s Brochure, Version 19 and Addenda 1 and 2, the following updates have been made:
  - The list of identified risks for atezolizumab has been revised to include myelitis, facial paresis, and pericardial disorders (Section 5.1.1).
  - 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 9 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.
  - Appendix 9 has been revised to include autoimmune myelitis.
  - The adverse event management guidelines have been updated to align with the Addendum 1 and Addendum 2 to the Atezolizumab Investigator's Brochure, Version 19 (Appendix 9).

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

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM 14

PROTOCOL SYNOPSIS 15

1. BACKGROUND 24

1.1 Background on HER2-Positive Breast cancer 24

1.2 Treatment of Early HER2-Positive Breast Cancer 25

1.3 Background on Atezolizumab 27

1.3.1 Clinical Experience with Atezolizumab in Triple-Negative Breast Cancer 27

1.3.2 Clinical Experience with Atezolizumab in HER2-Positive Breast Cancer 29

1.4 Study Rationale and Benefit–Risk Assessment 31

2. OBJECTIVES AND ENDPOINTS 35

2.1 Efficacy Objectives 35

2.1.1 Co-Primary Efficacy Objective 35

2.1.2 Secondary Efficacy Objectives 36

2.1.3 Exploratory Efficacy Objectives 36

2.2 Safety Objective 37

2.3 Pharmacokinetic Objective 37

2.4 Immunogenicity Objectives 37

2.5 Biomarker Objectives 38

3. STUDY DESIGN 38

3.1 Discontinuation of Experimental Treatment and Unblinding at Study Level 38

3.1.1 Implications of Unblinding on Study Design and Assessments 39

3.2 Description of the Study Prior to Stopping Blinded Treatment 39

3.2.1 Overview of Study Design 39

3.2.2 Independent Data Monitoring Committee 47

3.3 End of Study and Length of Study 47

3.4 Rationale for Study Design 47

3.4.1 Rationale for Atezolizumab Dose and Schedule 47

3.4.2 Rationale for Chemotherapy Choice and Schedule 48
3.4.3 Rationale for Patient Population 49
3.4.4 Rationale for Control Group and Combination with Atezolizumab 49
3.4.5 Rationale for Trastuzumab Emtansine in Combination with Atezolizumab as Adjuvant Treatment Option 50
3.4.6 Rationale for Pathologic Complete Response as Primary Endpoint 51
3.4.7 Rationale for Biomarker Assessments 51
3.4.8 Rationale for Patient-Reported Outcome Assessments 53
4. MATERIALS AND METHODS 55
4.1 Patients 55
4.1.1 Inclusion Criteria 55
4.1.2 Exclusion Criteria 58
4.2 Method of Treatment Assignment and Blinding 61
4.2.1 Treatment Assignment 61
4.2.2 Blinding 62
4.3 Study Treatment and Other Treatments Relevant to the Study Design 63
4.3.1 Study Treatment Formulation, Packaging, and Handling 63
4.3.1.1 Atezolizumab and Placebo 63
4.3.1.2 Pertuzumab (Perjeta®) 64
4.3.1.3 Trastuzumab (Herceptin®) 64
4.3.1.4 Trastuzumab Emtansine (Kadcyla®) 64
4.3.1.5 Chemotherapy 64
4.3.2 Study Treatment Dosage, Administration, and Compliance 64
4.3.2.1 Atezolizumab and Placebo 65
4.3.2.2 Pertuzumab (Perjeta®) 66
4.3.2.3 Trastuzumab (Herceptin®) 67
4.3.2.4 Trastuzumab Emtansine (Kadcyla®) 68
4.3.2.5 Chemotherapy 69
4.3.3 Other Required Medication 70
4.3.4 Investigational Medicinal Product Accountability 70

4.3.5 Continued Access to Atezolizumab, Pertuzumab, Trastuzumab, and Trastuzumab Emtansine 71
4.4 Concomitant Therapy 71
4.4.1 Permitted Therapy 71
4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients 74
4.4.2.1 Corticosteroids and TNF-α Inhibitors 74
4.4.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes 74
4.4.2.3 Herbal Therapies 75
4.4.2.4 *Therapies Given for Thrombocytopenia Induced by Chemotherapy* 75
4.4.3 Prohibited Therapy 75
4.5 Study Assessments 76
4.5.1 Informed Consent Forms and Screening Log 76
4.5.2 Medical History, Concomitant Medication, and Demographic Data 76
4.5.3 Physical Examinations 76
4.5.4 Vital Signs 77
4.5.5 Locoregional Tumor Status Assessments 77
4.5.6 Distant Sites Tumor Assessment 78
4.5.7 Disease Follow-Up and Confirmation of Disease Progression or Recurrence 79
4.5.8 Surgical Specimen Pathology 82
4.5.9 Laboratory, Biomarker, and Other Biological Samples 82
4.5.10 Electrocardiograms 85
4.5.11 Echocardiograms or Multiple-Gated Acquisition Scans 85
4.5.12 Patient-Reported Outcomes 85
4.5.12.1 EORTC QLQ-C30 86
4.5.12.2 FACT-G Single Item GP5 86
4.5.12.3 EQ-5D-5L 87
4.5.13 Samples for Whole Genome Sequencing 87
4.5.14 Optional Samples for Research Biosample Repository 88
4.5.14.1 Overview of the Research Biosample Repository 88
4.5.14.2 Approval by the Institutional Review Board or Ethics Committee 89

4.5.14.3 Sample Collection 89
4.5.14.4 Confidentiality 89
4.5.14.5 Consent to Participate in the Research Biosample Repository 90
4.5.14.6 Withdrawal from the Research Biosample Repository 90
4.5.14.7 Monitoring and Oversight 91
4.6 Treatment, Patient, Study, and Site Discontinuation 91
4.6.1 Study Treatment Discontinuation 91
4.6.2 Patient Discontinuation from Study 92
4.6.3 Partial Withdrawal from Study 92
4.6.4 Study Discontinuation 93
4.6.5 Site Discontinuation 93
5. ASSESSMENT OF SAFETY 93
5.1 Safety Plan 93
5.1.1 Risks Associated with Atezolizumab 94
5.1.2 Risks Associated with Doxorubicin 94
5.1.2.1 Cardiomyopathy 94
5.1.3 Risks Associated with Cyclophosphamide 95
5.1.4 Risks Associated with Paclitaxel 95
5.1.5 Risks Associated with Pertuzumab, Trastuzumab, and Trastuzumab Emtansine 96
5.1.5.1 Cardiotoxicity 97
5.1.5.2 EGFR-Related Toxicities 100
5.1.6 Risks Associated with Trastuzumab Emtansine 100
5.1.6.1 Pulmonary Toxicity 100
5.1.6.2 Hepatotoxicity 101
5.1.6.3 Left Ventricular Dysfunction 101
5.1.6.4 Infusion-Related Reactions and Hypersensitivity Reactions 102
5.1.6.5 Hematologic Toxicity 102
5.1.6.6 Hemorrhage 103
5.1.6.7 Neurotoxicity 103
5.1.6.8 Extravasation 103
5.1.7 Risks Associated with Combination Use of Pertuzumab with Trastuzumab and Paclitaxel 104

5.1.8 Risks Associated with Combination Use of Atezolizumab and Doxorubicin, Cyclophosphamide, Paclitaxel, Trastuzumab, Pertuzumab, or Trastuzumab Emtansine 105
5.1.9 General Plan to Manage Safety Concerns 107
5.1.10 Dose Modifications 107
5.1.10.1 Dose Modifications of Trastuzumab Emtansine and Atezolizumab/Placebo 108
5.2 Safety Parameters and Definitions 109
5.2.1 Adverse Events 110
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 110
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 111
5.2.4 Selected Adverse Events 112
5.2.4.1 Cardiac, General 112
5.2.4.2 Asymptomatic Left Ventricular Systolic Dysfunction 112
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 113
5.3.1 Adverse Event Reporting Period 114
5.3.2 Eliciting Adverse Event Information 114
5.3.3 Assessment of Severity of Adverse Events 114
5.3.4 Assessment of Causality of Adverse Events 115
5.3.5 Procedures for Recording Adverse Events 116
5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome 116
5.3.5.2 Diagnosis versus Signs and Symptoms 117
5.3.5.3 Adverse Events That Are Secondary to Other Events 117
5.3.5.4 Persistent or Recurrent Adverse Events 117
5.3.5.5 Abnormal Laboratory Values 118
5.3.5.6 Abnormal Vital Sign Values 119
5.3.5.7 Abnormal Liver Function Tests 119
5.3.5.8 Deaths 120
5.3.5.9 Preexisting Medical Conditions 120
5.3.5.10 Lack of Efficacy or Worsening of HER2-Positive Breast Cancer 120

5.3.5.11 Hospitalization or Prolonged Hospitalization 121
5.3.5.12 Patient-Reported Outcome Data 121
5.3.5.13 Safety Biomarker Data 121
5.4 Immediate Reporting Requirements from Investigator to Sponsor 121
5.4.1 Emergency Medical Contacts 122
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 122
5.4.2.1 Events That Occur prior to Study Treatment Initiation 122
5.4.2.2 Events That Occur after Study Treatment Initiation 122
5.4.3 Reporting Requirements for Pregnancies 123
5.4.3.1 Pregnancies in Female Patients 123
5.4.3.2 Pregnancies in Female Partners of Male Patients 124
5.4.3.3 Abortions 124
5.4.3.4 Congenital Anomalies/Birth Defects 124
5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error 125
5.5 Follow-Up of Patients after Adverse Events 126
5.5.1 Investigator Follow-Up 126
5.5.2 Sponsor Follow-Up 126
5.6 Adverse Events That Occur after the Adverse Event Reporting Period 126
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 127
6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 127
6.1 Analysis Populations 127
6.2 Determination of Sample Size 128
6.2.1 Type I Error Control 128
6.3 Summaries of Conduct of Study 128
6.4 Summaries of Demographic and Baseline Characteristics 129
6.5 Efficacy Analyses 129
6.5.1 Co-Primary Efficacy Endpoint 129
6.5.2 Secondary Efficacy Endpoints 130
6.5.2.1 pCR in the Subgroups 130

6.5.2.2 Event-Free Survival 130
6.5.2.3 Disease-Free Survival 131
6.5.2.4 Overall Survival 131
6.5.2.5 Patient-Reported Outcomes of Role and Physical Function and GHS/HRQoL: EORTC Data 132
6.5.3 Exploratory Efficacy Endpoints 132
6.5.3.1 Patient-Reported Outcomes of Disease/Treatment–Related Symptoms, and Emotional and Social Function: EORTC Data 132
6.5.3.2 Patient-Reported Outcome of Treatment Bother: FACT-G, GP5 Single-Item Data 132
6.5.3.3 Health Economic EQ-5D-5L Data 133
6.6 Safety Analyses 133
6.6.1 Exposure of Study Medication 133
6.6.2 Adverse Events 133
6.6.3 Laboratory Data 133
6.6.4 Vital Signs 134
6.7 Pharmacokinetic Analyses 134
6.8 Immunogenicity Analyses 134
6.9 Biomarker Analyses 135
6.10 Interim Analyses 135
6.10.1 Planned Interim Analyses 135
6.10.2 Optional Interim Analyses 135

7. DATA COLLECTION AND MANAGEMENT 136
7.1 Data Quality Assurance 136
7.2 Electronic Case Report Forms 136
7.3 Source Data Documentation 136
7.4 Use of Computerized Systems 137
7.5 Retention of Records 137

8. ETHICAL CONSIDERATIONS 138
8.1 Compliance with Laws and Regulations 138
8.2 Informed Consent 138
8.3 Institutional Review Board or Ethics Committee 139
8.4 Confidentiality 140

8.5 Financial Disclosure 140
9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 141
9.1 Study Documentation 141
9.2 Protocol Deviations 141
9.3 Management of Study Quality 141
9.4 Site Inspections 141
9.5 Administrative Structure 141
9.6 Dissemination of Data and Protection of Trade Secrets 142
9.7 Protocol Amendments 143
10. REFERENCES 143

LIST OF TABLES

Table 1 Administration of First and Subsequent Atezolizumab Infusions 66
Table 2 Administration of First and Subsequent Infusions of Trastuzumab Emtansine 68
Table 3 Hormonal Therapy 73
Table 4 Definitions of and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Events on Follow-Up 80
Table 5 Guidance for Managing Overlapping Toxicities 105
Table 6 Dose Modification Scheme for Trastuzumab Emtansine 109
Table 7 Reporting Conventions for Left Ventricular Systolic Dysfunction/Congestive Heart Failure 113
Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE 115
Table 9 Causal Attribution Guidance 116

LIST OF FIGURES

Figure 1 Study Schema 41
Figure 2 Documenting Treatment Burden in Patients with Early Breast Cancer 54
Figure 3 Algorithm for Continuation and Discontinuation of Study Treatment on the Basis of LVEF Assessment 99

LIST OF APPENDICES

Appendix 1 Schedule of Activities 152
Appendix 2 Schedule of Pharmacokinetic and Immunogenicity Samples ... 161
Appendix 3 Schedule of Blood and Tissue Samples for Biomarker Analysis 164
Appendix 4 European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30: EORTC QLQ-C30 166
Appendix 5 Functional Assessment of Cancer Therapy–General (FACT-G) Single-Item GP5 168
Appendix 6 EuroQol 5-Dimension, 5-Level Questionnaire: EQ-5D-5L 169
Appendix 7 Ventana HER2 IHC Assay 172
Appendix 8 Ventana HER2 ISH Assay 173
Appendix 9 Preexisting Autoimmune Diseases and Immune Deficiencies . 174
Appendix 10 Anaphylaxis Precautions 176
Appendix 11 Overall Guidelines for Management of Patients Who Experience Adverse Events 177
Appendix 12 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab 187
Appendix 13 Eastern Cooperative Oncology Group Scale of Performance Status 221
Appendix 14 Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine 222
Appendix 15 Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab 227

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH NEOADJUVANT DOXORUBICIN + CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL + TRASTUZUMAB + PERTUZUMAB IN EARLY HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	BO40747
VERSION NUMBER:	6
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NCT NUMBER:	NCT03726879
IND NUMBER:	123277
TEST PRODUCT:	Atezolizumab (RO5541267), Pertuzumab (RO4368451), Trastuzumab (RO0452317), Trastuzumab emtansine (RO5304020)
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH NEOADJUVANT DOXORUBICIN + CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL + TRASTUZUMAB + PERTUZUMAB IN EARLY HER2-POSITIVE BREAST CANCER**
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VERSION NUMBER:	6
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NCT NUMBER:	NCT03726879
IND NUMBER:	123277
TEST PRODUCT:	Atezolizumab (RO5541267), Pertuzumab (RO4368451), Trastuzumab (RO0452317), Trastuzumab emtansine (RO5304020)
PHASE:	Phase III
INDICATION:	Early HER2-positive breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

STUDY RATIONALE

This study (also known as IMpassion050) will evaluate the efficacy and safety of atezolizumab compared with placebo when given in combination with neoadjuvant dose-dense anthracycline (doxorubicin) + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab (ddAC-PacHP) in patients with early human epidermal growth factor 2 (HER2)-positive breast cancer at high risk of recurrence (T2–4, N1–3, M0).

OBJECTIVES AND ENDPOINTS

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

EFFICACY OBJECTIVES

CO-PRIMARY EFFICACY OBJECTIVE

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the early breast cancer (EBC) setting in the PD-L1–positive (IC 1/2/3) and the intent-to-treat (ITT) populations on the basis of the following endpoint:

- Pathological complete response (pCR), defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/is ypN0 in the current American Joint Committee on Cancer [AJCC] staging system, 8th edition) in the PD-L1–positive and ITT populations

SECONDARY EFFICACY OBJECTIVES

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the EBC setting on the basis of the following endpoints:
  - pCR (ypT0/is ypN0) based upon hormone receptor status (estrogen receptor [ER]/progesterone receptor [PgR] positive or ER/PgR negative)
  - pCR (ypT0/is ypN0) in the PD-L1–negative (IC 0) population
  - Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause, whichever occurs first, in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
  - Disease-free survival (DFS), defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first, in all patients who undergo surgery and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
  - Overall survival (OS), defined as the time from randomization to death from any cause in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- To evaluate patient-reported outcomes (PROs) of function (role, physical) and health-related quality of life (HRQoL) associated with atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), on the basis of the following endpoint:
  - Mean and mean changes from baseline score in function (role, physical) and global health status (GHS)/HRQoL by assessment timepoint, and between treatment arms as assessed by the functional and GHS/HRQoL scales of the EORTC QLQ-C30

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the neoadjuvant setting and the safety of atezolizumab combined with trastuzumab + pertuzumab (or combined with trastuzumab emtansine) compared with placebo combined with trastuzumab + pertuzumab (or combined with trastuzumab emtansine) in the adjuvant EBC setting on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of atezolizumab, pertuzumab, and trastuzumab when given in combination and of atezolizumab and trastuzumab emtansine when given in combination on the basis of the following endpoints:

- Peak and trough (maximum serum concentration observed [C_{max}] and minimum serum concentration under steady-state conditions within a dosing interval [C_{min}]) of atezolizumab concentrations in serum at specified timepoints
- Trough concentration for pertuzumab and trastuzumab in serum at specified timepoints
- Peak and trough concentration for trastuzumab emtansine in serum at specified timepoints

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab, trastuzumab, pertuzumab, and trastuzumab emtansine on the basis of the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs) to atezolizumab and its impact on pharmacokinetics, efficacy, and safety
- Incidence of treatment-emergent ADAs to trastuzumab, pertuzumab, and trastuzumab emtansine

BIOMARKER OBJECTIVES

The secondary biomarker objectives for this study are as follows:

- To evaluate pCR (ypT0/is ypN0), EFS, DFS, and OS based upon PIK3CA mutation status

OVERALL **DESIGN** *AND STUDY POPULATION*

DISCONTINUATION OF EXPERIMENTAL TREATMENT AND UNBLINDING AT STUDY LEVEL

On 26 January 2021, the independent Data Monitoring Committee (iDMC) met and conducted a review of unblinded safety and efficacy data. Following their review of the data, the iDMC recommended to stop randomized treatment assignment with atezolizumab or placebo. Study treatment without atezolizumab/placebo should be continued through the completion of the adjuvant treatment phase. On 3 February 2021, the Sponsor issued an "Urgent Safety Measure Dear Investigator Letter" (USM DIL) communicating the request to stop treatment with atezolizumab or placebo and informed about the unblinding of the study.

The addition of atezolizumab did not result in an increase in the pCR rate compared with the control arm both in the ITT and the PD-L1–positive population. There were four Grade 5 adverse events in the atezolizumab arm, which occurred in the neoadjuvant phase. The iDMC commented that the difference in death between the two arms was not significant but in the margin of significance. Considering that the majority of the patients had undergone surgery, their recommendation was to stop the atezolizumab/placebo treatment administration from an ethical perspective.

IMPLICATIONS OF UNBLINDING ON STUDY DESIGN AND ASSESSMENTS

Following the discontinuation of atezolizumab or placebo, patients should continue all other study drugs without atezolizumab or placebo and follow study assessments and follow-up assessments as described in the protocol. Following the implementation of Protocol Version 5, the PK and ADA sample collection for atezolizumab, trastuzumab and pertuzumab (or trastuzumab emtansine) is only required at the treatment discontinuation visit.

The study was unblinded on 5 February 2021 and the unblinding date will be used as the clinical cutoff date for the primary analysis. As per Statistical Analysis Plan, patients with missing pCR assessment will be counted as not achieving pCR in the analysis; this includes patients who have not yet undergone surgery and pCR assessment due to the early unblinding of the study. Patients who are still in the neoadjuvant phase of the study at the time of unblinding should continue their study treatment without atezolizumab or placebo and undergo surgery and pathological assessment as per study protocol followed by the adjuvant study phase with study treatment excluding atezolizumab or placebo.

OVERVIEW OF STUDY DESIGN PRIOR TO STOPPING BLINDED TREATMENT

This is a global Phase III, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PacHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3, M0).

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase III*	***Population Type:***	*Adult patients*
Control Method:	*Placebo*	***Population Diagnosis or Condition:***	*Early HER2-positive breast cancer*
Interventional Model:	*Parallel group*	***Population Age:***	*≥18 years of age*
Test Compounds:	*Atezolizumab (RO5541267), Pertuzumab (RO4368451), Trastuzumab (RO0452317), Trastuzumab emtansine (RO5304020)*	***Site Distribution:***	*Multi-site*
Active Comparator:	*Not applicable*	***Study Intervention Assignment Method:***	*Randomization and stratification*
Number of Arms:	*Two*	***Number of Participants to Be Enrolled:***	*Approximately 453*

STUDY TREATMENT

The investigational medicinal products for this study are atezolizumab, trastuzumab, pertuzumab, trastuzumab emtansine, doxorubicin, cyclophosphamide, and paclitaxel.

ATEZOLIZUMAB AND PLACEBO

During the neoadjuvant phase, atezolizumab/placebo will be administered by IV infusion at a fixed dose of 840 mg on Day 1 of each 14-day cycle during Cycles 1–4, and 1200 mg on Day 1 of each 21-day cycle during Cycles 5–8. During the adjuvant phase (postoperatively), atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (maximum of 22 cycles [neoadjuvant + adjuvant phases]). Atezolizumab/placebo should be administered as the first infusion.

Treatment will continue as scheduled or until disease progression, recurrence of disease, or unmanageable toxicity.

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 the protocol. Atezolizumab infusions will be administered per the instructions outlined in the protocol.

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 the protocol.

No dose modification for atezolizumab is allowed.

PERTUZUMAB

Pertuzumab is given as a fixed non–weight-based dose of 840-mg IV loading dose, then 420 mg IV Q3W. Pertuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. Atezolizumab/placebo should be administered prior to pertuzumab and trastuzumab. The order of administration of pertuzumab and trastuzumab is according to investigator preference.

The initial dose of pertuzumab will be administered over 60 (±10) minutes, and patients will be observed for a further 60 minutes. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 (±10) minutes, and patients will be observed for a further 30 minutes for infusion-related symptoms such as fever or chills. All infusion-related symptoms must have resolved before trastuzumab or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in the protocol. No dose reductions are allowed for pertuzumab. If the patient misses a dose of pertuzumab for any cycle and the time between doses is ≥6 weeks, a reloading dose of pertuzumab (840 mg) should be given. Subsequent maintenance pertuzumab (420 mg) will then be given Q3W, starting 3 weeks later.

If the interval between the first dose of adjuvant pertuzumab and the last dose of neoadjuvant pertuzumab is 6 weeks or more, a reloading dose of 840 mg of pertuzumab is required.

TRASTUZUMAB

Trastuzumab is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. Trastuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. Atezolizumab/placebo should be administered prior to pertuzumab and trastuzumab. The order of administration of pertuzumab and trastuzumab is according to investigator preference.

Weight should be recorded during screening and on Day 1 of each cycle for all patients. The baseline weight for a patient will be that measured on Cycle 1, Day 1. The amount of trastuzumab to be administered must be recalculated if the patient's body weight has changed by >10% (increased or decreased) from the Cycle 1, Day 1 weight. The amount of trastuzumab administered is calculated according to the patient's actual body weight, with no upper limit.

The initial dose of trastuzumab will be administered over 90 (±10) minutes, and patients will be observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever or chills. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (±10) minutes, and patients will be observed for a further 30 minutes. All infusion-related symptoms must have resolved before pertuzumab or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in the protocol. No dose reductions are allowed for trastuzumab. If the patient misses a dose of trastuzumab for any cycle and the time between doses is ≥6 weeks, a reloading dose of trastuzumab (8 mg/kg) should be given. Subsequent maintenance trastuzumab (6 mg/kg) doses will then be given Q3W, starting 3 weeks later.

If the interval between the first dose of adjuvant trastuzumab and the last dose of neoadjuvant trastuzumab is 6 weeks or more, a reloading dose of 8 mg/kg of trastuzumab is required.

TRASTUZUMAB EMTANSINE

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W. The dose of trastuzumab emtansine administered will be determined on the basis of the baseline weight of the patient. Weight will be measured at each visit and the dose must be re-adjusted for weight changes ≥10% compared with the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, in accordance to local practice. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed, following the dose reduction levels provided in the protocol. Once a dose has been reduced for an adverse event(s), it must not be re-escalated.

Trastuzumab emtansine should be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Trastuzumab emtansine will be administered after the infusion of atezolizumab or placebo.

CHEMOTHERAPY

Chemotherapy will be administered in the neoadjuvant setting as follows:

- Doxorubicin 60 mg/m^2 IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4); with
- Cyclophosphamide 600 mg/m^2 IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4); followed by
- Paclitaxel 80 mg/m^2 IV weekly for 12 continuous weeks (Cycles 5–8)

The dose of chemotherapy is calculated according to the patient's BSA. The BSA and the amount of drug administered must be recalculated if the patient's body weight has changed by > 10% (increased or decreased) from baseline. Recalculation of the amount of drug administered on the basis of smaller changes in body weight or BSA is at the investigators' discretion.

There is no mandatory delay between atezolizumab/placebo and ddAC chemotherapy, assuming the infusion is well tolerated.

See the protocol for details on the dosage and administration of doxorubicin, cyclophosphamide, and paclitaxel.

DURATION OF PARTICIPATION

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 54 months, assuming a recruitment period of approximately 18 months, and follow-up for 36 months from the date of enrollment of the last patient in the study.

COMMITTEES

Independent Committees:	*Independent Data Monitoring Committee*
Other Committees:	*Not applicable*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also called anti-therapeutic antibody
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
AV	atrioventricular
BSA	body surface area
C_{max}	maximum serum concentration observed
C_{min}	minimum serum concentration under steady-state conditions within a dosing interval
COPD	chronic obstructive pulmonary disease
CSR	Clinical Study Report
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating-tumor DNA
ddAC	dose-dense anthracycline (doxorubicin + cyclophosphamide)
ddAC-PacHP	dose-dense anthracycline (doxorubicin + cyclophosphamide) followed by paclitaxel + trastuzumab + pertuzumab
DFS	disease-free survival
DLT	dose-limiting toxicity
EBC	early breast cancer
EC	Ethics Committee
eCRF	electronic Case Report Form
ECHO	echocardiogram
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension, 5-Level (questionnaire)
ER	estrogen receptor
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy–General
FDA	Food and Drug Administration
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
FFPE	formalin-fixed, paraffin-embedded
G-CSF	granulocyte colony–stimulating factor

Abbreviation	Definition
EGFR	epidermal growth factor receptor
GHS	global health status
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cell
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IL-2	interleukin-2
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
NE	not evaluable
LN	lymph node
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
NAST	neoadjuvant systemic therapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing

Abbreviation	Definition
NRH	nodular regenerative hyperplasia
NSCLC	non–small cell lung cancer
NYHA	New York Heart Association
OS	overall survival
PacHP	paclitaxel + trastuzumab + pertuzumab
pCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-C30	Quality-of-Life Questionnaire–Core 30
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SOC	standard-of-care
T3	triiodothyronine
TC	tumor cell
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor-α
ULN	upper limit of normal
USM DIL	Urgent Safety Measure Dear Investigator Letter
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE BREAST CANCER

Globally, breast cancer is the second most common invasive malignancy and the most common cause of cancer-related mortality in women. An estimated 1.7 million new breast cancer cases were diagnosed in 2012 (25% of all cancers in women) and there were 521,900 deaths (DeSantis et al. 2015; Ferlay et al. 2015). The majority of breast cancers in the Western world is 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. 2013; 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.

Approximately 1 in 5 women diagnosed with EBC will have human epidermal growth factor 2 (HER2)-positive disease (Wolff et al. 2013). Breast cancers over-expressing HER2 are the most aggressive, and while current therapies have improved patient outcomes, up to 1 in 4 women with HER2-positive EBC will experience recurrence or death within 10–11 years of diagnosis, despite treatment with adjuvant trastuzumab plus standard chemotherapy (Perez et al. 2014; Slamon et al. 2016; Cameron et al. 2017). In those patients treated with neoadjuvant trastuzumab and pertuzumab with standard chemotherapy, 5-year disease-free survival (DFS) rates sit at 84% (Gianni et al. 2016).

Patients who relapse with metastatic or unresectable disease are generally incurable. Overall (i.e., all subtypes of breast cancer, including HER2-negative disease), patients with metastatic disease have a median survival of approximately 24 months and a 5-year life expectancy of 18%–26% in the United States and Europe (Sant et al. 2003; Howlader et al. 2016). With the advent of pertuzumab, life expectancy for patients with metastatic HER2-positive breast cancer has greatly improved with an observed median overall survival (OS) of 56.5 months in the CLEOPATRA study. Nevertheless, more than 50% of patients receiving first-line treatment with trastuzumab, pertuzumab, and a taxane for metastatic disease die within 5 years (Swain et al. 2015).

New active agents are still required for patients with HER2-positive breast cancer, which is estimated to account for approximately 6,000–8,000 deaths per year in the United States, 19,000–26,000 deaths per year in Europe, and approximately 78,000–104,000 deaths per year globally (DeSantis et al. 2015; Ferlay et al. 2015; Howlader et al. 2016). Since metastatic disease is currently incurable, improving the results of initial therapy, when the disease is still localized to the breast and regional lymph nodes but without distant metastases offers the best chance of cure. For patients who are not cured, improved initial therapy may also produce meaningful delays in disease recurrence and death.

1.2 TREATMENT OF EARLY HER2-POSITIVE BREAST CANCER

The treatment and prognosis of patients with HER2-positive breast cancer have been transformed by the advent of HER2-targeted agents. The humanized monoclonal antibody trastuzumab (Herceptin®), which binds to the extracellular domain of HER2, is approved for use as a single agent or in combination with chemotherapy or hormonal therapy in the metastatic setting, and as (neo)adjuvant treatment for patients with early-stage HER2-positive breast cancer. Globally, trastuzumab-based therapy is the recommended treatment for patients with HER2-positive early-stage breast cancer who do not have contraindications for its use (Herceptin Prescribing Information; European Society for Medical Oncology [ESMO] guidelines [Senkus et al. 2015]; National Comprehensive Cancer Network [NCCN] Guidelines, Version 1.2017 [Gradishar et al. 2017]).

An improvement to standard trastuzumab therapy for HER2-positive EBC comes with the addition of another HER2-targeted therapy, pertuzumab (Perjeta®), approved in many countries for the treatment of HER2-positive metastatic breast cancer and for neoadjuvant use in patients with high-risk, HER2-positive EBC. This combination has been adopted in global guidelines for use in these patients in the neoadjuvant setting (Perjeta Prescribing Information; ESMO guidelines [Senkus et al. 2015]; NCCN Guidelines, Version 1.2017 [Gradishar et al. 2017]). Pertuzumab has also been recently approved in the United States, Europe, and other countries throughout the world for post-surgery (adjuvant) treatment of HER2-positive EBC at high risk of recurrence (Perjeta Prescribing Information; NCCN 2019; Hammond et al. 2010).

In HER2-positive EBC, neoadjuvant pertuzumab + trastuzumab + docetaxel provides a statistically significant and clinically meaningful improvement in pathological complete response (pCR) rates over trastuzumab + docetaxel alone (45.8% vs. 29.0%; $p = 0.0141$; Gianni et al. 2012). Patients in this study went on to receive additional chemotherapy following surgery regardless of pCR status. In a descriptive analysis, 5-year DFS rates were reported to be higher in those patients who received neoadjuvant pertuzumab + trastuzumab + docetaxel than those patients who received trastuzumab + docetaxel alone (hazard ratio [HR] = 0.60; 0.28–1.27). In a study in which neoadjuvant pertuzumab and trastuzumab were evaluated with either anthracycline-based chemotherapy or carboplatin-based chemotherapy, pCR rates (ypT0/is, ypN0 in the current American Joint Committee on Cancer [AJCC] staging system) for all regimens ranged from 57.3%–66.2%, with the highest pCR rate being achieved in the docetaxel + carboplatin + trastuzumab + pertuzumab regimen (Schneeweiss et al. 2013). Supporting these results, in the BERENICE study (Study WO29217), pCR (ypT0/is, ypN0) rates in two neoadjuvant regimens containing pertuzumab + trastuzumab + taxane and chemotherapy were high in both treatment arms (61.8% [Cohort A; dose-dense doxorubicin and cyclophosphamide (ddAC)-taxane]) and 60.7% [Cohort B; 5-fluorouracil, epirubicin, and cyclophosphamide (FEC)-taxane]; Swain et al. 2018).

Neratinib (Nerlynx®) is a HER2-targeted tyrosine kinase inhibitor that has recently been approved for use in the United States as additional adjuvant therapy in patients with early-stage HER2-positive breast cancer (Nerlynx Prescribing Information; Chan et al. 2016]).

Trastuzumab emtansine is an approved treatment for patients with HER2-positive advanced breast cancer who have received therapy with trastuzumab and a taxane and who have received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy (Verma et al 2012; NCCN 2019). Study BO27938 (Katherine) was designed to investigate the effect of trastuzumab emtansine in patients with HER2-positive early breast cancer. The study was a randomized, multicenter, open-label Phase III study to evaluate the efficacy and safety of trastuzumab emtansine compared with trastuzumab as adjuvant therapy for patients with HER2-positive early breast cancer who have residual tumor present in the breast or axillary lymph nodes following neoadjuvant therapy containing a taxane and trastuzumab. Results showed that invasive DFS was significantly improved with trastuzumab emtansine compared with trastuzumab (HR = 0.50; 95% CI: 0.39 to 0.64; $p < 0.001$; von Minckwitz et al 2019). The estimated percentage of patients free of invasive disease at 3 years from randomization was 88.3% with trastuzumab emtansine and 77.0% with trastuzumab. A higher proportion of patients receiving trastuzumab emtansine compared with patients receiving trastuzumab experienced Grade ≥ 3 adverse events (25.7% vs. 15.4%), serious adverse events (12.7% vs. 8.1%), and adverse events leading to discontinuation of study drug (18.0% vs. 2.1%). The proportion of patients receiving adjuvant radiotherapy was 84.2% in the trastuzumab emtansine arm and 81.9% in the trastuzumab arm (Primary Clinical Study Report [CSR] Study BO27938, Report Number 1087528, January 2019). Higher rates of pulmonary toxicities, including pneumonitis and radiation pneumonitis, were reported in the trastuzumab emtansine arm (21 patients; 2.8%) compared with the trastuzumab arm (6 patients; 0.8%). In the trastuzumab emtansine arm, 1.5% of patients (n = 11) experienced radiation pneumonitis, 1.1% of patients (n = 8) experienced pneumonitis, 0.1% of patients (n = 1) experienced pulmonary fibrosis, and 0.1% of patients (n = 1) experienced pulmonary radiation injury. In the trastuzumab arm, 0.7% of patients (n = 5) experienced radiation pneumonitis, 0.1% of patients (n = 1) experienced pneumonitis; no patient experienced pulmonary fibrosis or pulmonary radiation injury. In the trastuzumab emtansine arm, the majority of patients (18 of 21) experienced pulmonary toxicities of Grade 1 or 2. Of the 11 patients in the trastuzumab emtansine arm who experienced radiation pneumonitis, the event was Grade 1 or 2 in 9 patients; 2 patients experienced Grade 3 events. All events of radiation pneumonitis resolved and were reported in patients who received radiation concurrent with adjuvant trastuzumab emtansine. Of the 8 patients in the trastuzumab emtansine arm who experienced pneumonitis, the event was Grade 1 or 2 in 7 patients; 1 patient experienced a Grade 3 event of pneumonitis. Trastuzumab emtansine was withdrawn in all but one patient who experienced pneumonitis and all events resolved or resolved with sequelae

(Primary CSR Study BO27938, Report Number 1087528, January 2019). Based on the results of the Katherine study, the U.S. Food and Drug Administration (FDA) and European Commission have approved trastuzumab emtansine in the adjuvant setting for patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small cell lung cancer, hepatocellular carcinoma, melanoma, and triple-negative breast cancer (TNBC). Refer to the atezolizumab Investigator's Brochure for further details.

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 in multiple indications. See the Atezolizumab Investigator's Brochure for full study descriptions and available data.

The available safety and efficacy data in TNBC are primarily from three studies:

- Study PCD4989g is 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. Data from the TNBC cohort have been reported and demonstrate promising safety and efficacy results regardless of line of therapy and PD-L1 expression (Schmid et al. 2017).

- Study GP28328 is 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. Data from Arm F have been submitted for publication and support the use of atezolizumab in combination with chemotherapy in patients with TNBC. Confirmed responses were seen in 53.8% (95% CI: 25.1% to 80.8%) of patients with first-line metastatic TNBC and 39.4% (95% CI: 22.9% to 57.98%) of all patients regardless of line of therapy and PD-L1 expression. No new safety signals were seen (Adams et al. 2016). 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, and these responses may reasonably occur in tumors regardless of PD-L1 expression (Merritt et al. 2003; Apetoh et al. 2007).
- Study WO29522 (IMpassion130) is a Phase III, global, multicenter, double-blind, two-arm, randomized, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab administered with nab-paclitaxel in patients with metastatic or unresectable locally advanced TNBC who have not received prior systemic therapy for metastatic breast cancer. At the final analysis of progression-free survival (PFS) in the intent-to-treat (ITT) and the PD-L1–positive patient population, a statistically significant benefit was observed with the addition of atezolizumab to nab-paclitaxel with a median PFS of 5.5 months in the control arm and 7.2 months in the experimental arm (HR = 0.80; 95% CI, 0.69–0.92; p = 0.002) in the ITT population and a median PFS of 5.0 months in the control arm and 7.5 months in the experimental arm (HR = 0.62; 95% CI: 0.49 to 0.78; $p < 0.001$) in the PD-L1–positive population (Schmid et al. 2018).

  An interim analysis of OS was performed. The 16% reduction in the risk of death with atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel did not cross the interim boundary for statistical significance (HR: 0.759, available $\alpha = 0.0065$), with a stratified HR of 0.84; 95% CI: 0.69 to 1.02; p = 0.0840. The Kaplan-Meier estimated median OS was nearly 4 months longer in the atezolizumab + nab-paclitaxel arm (21.3 months vs. 17.6 months in the placebo + nab-paclitaxel arm). No formal testing of OS was performed in the PD-L1–positive population because hierarchy of testing indicates formal testing can only occur if OS is statistically significant in the ITT population first. However, OS results were unprecedented in the PD-L1–positive population. A clinically meaningful reduction in the risk of death of 38% was observed with atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel (stratified HR = 0.62; 95% CI: 0.45 to 0.86). This was accompanied by a 10-month prolongation in the Kaplan-Meier estimated median OS in the atezolizumab + nab-paclitaxel arm (25.0 months vs. 15.5 months placebo + nab-paclitaxel).

- Safety results from IMpassion130 are consistent with the known safety profile of atezolizumab monotherapy and atezolizumab in combination therapy, with no new safety concerns observed. The overall safety profile of atezolizumab and nab-paclitaxel is concordant between the PD-L1–positive and the overall safety-evaluable population.

Ongoing studies exploring atezolizumab combinations in TNBC include the following:

- Study WO39392 (IMpassion031) is a Phase III, randomized, placebo-controlled study evaluating the safety and efficacy of neoadjuvant nab-paclitaxel followed by dose-dense doxorubicin and cyclophosphamide administered in combination with either atezolizumab or placebo in early TNBC.
- Study WO39391 (IMpassion030) is a Phase III, randomized study evaluating the safety and efficacy of adjuvant paclitaxel followed by dose-dense anthracycline and cyclophosphamide with or without atezolizumab in early TNBC.
- Study NSABP B-59/GBG 96-GeparDouze is a randomized, double-blind Phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo in patients with TNBC followed by adjuvant atezolizumab or placebo (Geyer et al. 2018).

1.3.2 Clinical Experience with Atezolizumab in HER2-Positive Breast Cancer

Ongoing studies exploring atezolizumab combinations in HER2-positive patients include the following:

- Study GO29831 is a Phase Ib open-label, multi-cohort study. This study includes cohorts that evaluate the safety and pharmacokinetics of atezolizumab in combination with trastuzumab and pertuzumab or atezolizumab in combination with trastuzumab emtansine in patients with HER2-positive breast cancer. Enrollment in the study has been completed with a total of 73 patients with HER2-positive breast cancer (early or metastatic).
  - Cohort 1A has enrolled 6 patients with HER2-positive metastatic breast cancer who received atezolizumab in combination with trastuzumab and pertuzumab. After 6 patients in Cohort 1A were treated for at least 1 cycle, no patients experienced a dose-limiting toxicity (DLT).
  - Cohort 1F has enrolled a total of 6 patients with HER2-positive metastatic breast cancer who received atezolizumab in combination with docetaxel, trastuzumab, and pertuzumab. There was 1 patient among the first 3 patients enrolled in Cohort 1F who experienced an event that met the protocol definition of a DLT. However, stopping rules for enrollment to Cohort 1F as defined in the protocol were not met and enrollment of the remaining 3 patients was completed.
  - Cohort 2D has enrolled 1 patient with HER2-positive metastatic breast cancer who received atezolizumab in combination with trastuzumab and pertuzumab. This cohort was subsequently closed for resource alignment reasons unrelated to patient safety and efficacy.

- Cohort 2A has enrolled a total of 20 patients with HER2-positive EBC who received 2 cycles of atezolizumab in combination with trastuzumab and pertuzumab with sequential tumor biopsies for biomarkers, followed by standard-of-care (SOC) pre-operative docetaxel, carboplatin, trastuzumab, and pertuzumab and surgery. Cohort 2B has enrolled 20 patients with HER2-positive EBC who received 2 cycles of atezolizumab in combination with trastuzumab emtansine with sequential tumor biopsies for biomarkers, followed by SOC pre-operative docetaxel, carboplatin, trastuzumab, and pertuzumab and surgery.
- Additional cohorts with patients with HER2-positive metastatic breast cancer are Cohorts 1B (n = 6; safety run-in cohort; atezolizumab + trastuzumab emtansine) and 2C (n = 14; expansion cohort; atezolizumab + trastuzumab emtansine).

With a data cut-off of 17 December 2018, there have been no new safety signals overall emerging in the HER2-positive cohorts of Study GO29831, and adverse events are in line with the known safety profile of the individual components of the regimens being evaluated.

- Study WO30085 (Kate2) is a Phase II randomized study of trastuzumab emtansine with or without atezolizumab in HER2-positive, locally advanced unresectable or metastatic breast cancer with prior exposure to a taxane and trastuzumab. This study enrolled 202 patients.
  - On 22 November 2017, the independent Data Monitoring Committee (iDMC) met and conducted a pre-planned benefit–risk analysis. Following this analysis, the iDMC recommended to the Sponsor that the study be unblinded with respect to treatment assignment to allow investigators and patients to have an open discussion of the potential benefits and risks of continuing the experimental therapy. Unblinding was based upon the improbability of meeting the progression-free survival endpoint, numerically higher rates of serious adverse events that included one fatal event (hemophagocytic syndrome), and numerically higher adverse events leading to discontinuation of study drugs in the atezolizumab arm. The Sponsor issued a "Dear Investigator Letter" on 11 December 2017 communicating the unblinding of the study.
  - The clinical cutoff date for the primary efficacy analysis was 11 December 2017, at which time 107 PFS events had occurred in the ITT population. For the primary endpoint of PFS based on investigator assessment, the study did not demonstrate a meaningful PFS benefit from the addition of atezolizumab to trastuzumab emtansine in the ITT population. The stratified hazard ratio was 0.82 (95% CI: 0.55 to 1.23; p = 0.3332). The median PFS for trastuzumab emtansine + placebo was 6.8 months (95% CI: 4.0 to 11.1) and for trastuzumab emtansine + atezolizumab 8.2 months (95% CI: 5.8 to 10.7). The OS data were immature with a low event rate (11.6% in the trastuzumab emtansine + placebo arm vs. 9.8% in the trastuzumab emtansine + atezolizumab arm).

- The subgroup results of the PFS analysis suggested potential benefit of the trastuzumab emtansine + atezolizumab arm in the PD-L1–selected subgroup (tumor-infiltrating immune cell [IC] 1/2/3), although the magnitude of the benefit is uncertain given the limited number of patients and the observed imbalances in confounding factors. The stratified hazard ratio of PFS assessment in the PD-L1–selected subgroup was lower (HR: 0.60; 95% CI: 0.32 to 1.11; p = 0.0987) compared with the results of the PFS analysis in the ITT population. The median PFS in PD-L1–selected patients for trastuzumab emtansine + placebo was 4.1 months (2.7; 11.1) versus 8.5 months (5.7; not evaluable [NE]) with trastuzumab emtansine + atezolizumab.
- The safety profile of the combination was consistent with the known profiles of each study drug, and adverse events for the combination were manageable. Although the incidence of Grade ≥ 3 adverse events was similar between arms with 43.9% in the experimental arm and 41.2% in the control arm, thrombocytopenia, AST elevation, anemia, and pyrexia were numerically increased in the combination arm. A higher incidence of serious adverse events, of adverse events leading to atezolizumab or placebo discontinuation, and of adverse events leading to dose reduction of trastuzumab emtansine was reported in the combination arm. A total of 13 patients (19.1%) in the trastuzumab emtansine + placebo arm experienced at least one serious adverse event compared with 43 patients (32.6%) in the trastuzumab emtansine + atezolizumab arm. The most common serious adverse event reported in the trastuzumab emtansine + atezolizumab arm was pyrexia (10 patients [7.6%]), which was mostly driven by hospitalization for Grade 1 or 2 pyrexia (5.3%), 2 patients (1.5%) experienced Grade 3 pyrexia, and 1 patient (0.8%) experienced Grade 4 pyrexia; all 10 patients were reported to have recovered. The most common serious adverse events in the trastuzumab emtansine + placebo arm were seizure (2 patients [2.9%]) and abdominal pain (2 patients [2.9%]). One patient in the experimental arm experienced a fatal hemophagocytic syndrome. For the trastuzumab emtansine–selected adverse events, the incidence of thrombocytopenia, hepatotoxicity, peripheral neuropathy, and infusion-related reaction or hypersensitivity Type 1 were numerically increased in the trastuzumab emtansine + atezolizumab arm. For the atezolizumab adverse events of special interest, the incidence of immune-mediated hypothyroidism, immune-mediated colitis, immune-mediated rash, and immune-mediated ocular inflammatory toxicity were numerically increased in the trastuzumab emtansine + atezolizumab arm compared with the trastuzumab emtansine + placebo arm.

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 advanced malignancies (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 a transmembrane 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 anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed SOC therapies. Objective responses have been observed across a broad range of malignancies, including 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). More recently, clinically meaningful improvement of OS with atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel was observed in the Phase III Study WO29522 (IMpassion130) in patients with PD-L1–positive advanced TNBC (Schmid et al. 2018).

While cancer immunotherapy has demonstrated impressive results in patients with advanced malignancies, emerging data suggest that responses to cancer immunotherapy may be better when agents are administered in early-stage cancers, where higher levels of tumor-infiltrating lymphocytes (TILs) may be present (Lee et al. 2017; Loi et al. 2017). In particular, this may be more relevant in tumors where TILs are a prognostic factor, such as in early HER2-positive breast cancer.

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

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

The subtype of breast cancers over-expressing HER2 is the most aggressive. While current therapies have significantly improved patient outcomes, up to 1 in 4 women with HER2-positive EBC will experience recurrence or death within 10 to 11 years of diagnosis, despite treatment with adjuvant trastuzumab plus standard chemotherapy (Perez et al. 2014; Slamon et al. 2016; Cameron et al. 2017). Patients who received neoadjuvant trastuzumab and pertuzumab with standard chemotherapy, a patient group with tumor size >2 cm and who are considered at higher risk for recurrence, have demonstrated pCR rates ranging from 45%–68% (Gianni et al. 2012; Schneeweiss et al. 2013; Untch et al. 2016; van Ramshorst et al. 2017; Swain et al. 2018). Even with such rates, 5-year DFS rates in these patients are around 84% and are expected to be lower in those who are node positive (Gianni et al. 2012). More recently, data from the APHINITY study have demonstrated high invasive DFS rates at 3 years (94.1%) and 4 years (92.3%) with adjuvant trastuzumab and pertuzumab plus chemotherapy (von Minckwitz et al. 2017). However, in patients with node-positive disease, these values were numerically lower at both 3 years (92%) and 4 years (89.9%). As such, there is an opportunity to improve pCR rates and long-term outcomes for patients with high-risk, HER2-positive breast cancer.

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 the 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 has been investigated or is currently being investigated as part of several studies including Studies GP28328, GO29436 (IMpower150), GO29537 (IMpower130), GO30140, WO29522 (IMpassion130), WO39392 (IMpassion031), and WO39391 (IMpassion030). Atezolizumab in combination with chemotherapeutic regimens including anthracyclines and cyclophosphamide is currently being investigated as part of Studies BO29563, GO29831, WO39392 (IMpassion031), and WO39391 (IMpassion030). Thus far, reported adverse events observed were similar to those experienced with the individual components of the study treatment and have generally been manageable.

See Sections 1.3.1 and 1.3.2 and the Atezolizumab Investigator's Brochure for additional details. Atezolizumab in combination with pertuzumab and trastuzumab is currently being investigated as part of Study GO29831. No new safety signals have been reported and the study is ongoing.

The risk of overlapping toxicities between atezolizumab and doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab, and trastuzumab emtansine is thought to be manageable based on the mechanism of action of each product. In order to evaluate any potential risks associated with this combination regimen, a safety review of the first 12 patients enrolled (approximately 6 patients per arm) will be performed by the Sponsor and iDMC (without stopping accrual) after completion of 4 cycles of atezolizumab/placebo and doxorubicin + cyclophosphamide chemotherapy and 2 cycles of atezolizumab/placebo and paclitaxel + trastuzumab + pertuzumab chemotherapy. Furthermore, the first 26 patients of the study will be part of the safety cohort that will be closely monitored with additional cardiac monitoring (see Appendix 1). To reduce the risk of cardiac dysfunction with the combination used in this study, patients with cardiopulmonary dysfunction will be excluded from the study. Cardiac function will be closely monitored for all patients, including regular measurements of left ventricular ejection fraction (LVEF) throughout the study. An iDMC will regularly review unblinded safety data (see Section 3.2.2).

This trial will enroll patients with early (T2–4, N1–3, M0) HER2-positive breast cancer. HER2 status of the tumor will be centrally confirmed. The study population will be such that the final population will contain no more than 50% of patients with hormone receptor–positive disease. Given the rate of recurrence for these patients with very high-risk HER2-positive breast cancer, this population is considered appropriate for trials of novel therapeutic candidates. On the basis of recent results from Study BO27938, trastuzumab emtansine has been added as a recommended treatment option in the adjuvant setting for patients who do not achieve pCR and will be given in combination with atezolizumab/placebo. The anticipated benefit–risk ratio for atezolizumab in combination with trastuzumab, pertuzumab, chemotherapy, and trastuzumab emtansine is expected to be acceptable in this setting.

In the setting of the 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-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from 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.

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

2. OBJECTIVES AND ENDPOINTS

This study (also known as IMpassion050) will evaluate the efficacy and safety of atezolizumab compared with placebo when given in combination with neoadjuvant dose-dense anthracycline (doxorubicin) + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab (ddAC-PacHP) in patients with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3, M0). Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Co-Primary Efficacy Objective

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the EBC setting in the PD-L1–positive (IC 1/2/3) and the ITT population on the basis of the following endpoint:

- pCR, defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (NAST; i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition) in the PD-L1–positive and ITT populations

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the EBC setting on the basis of the following endpoints:
  - pCR (ypT0/is ypN0) based upon hormone receptor status (estrogen receptor [ER]/progesterone receptor [PgR] positive or ER/PgR negative)
  - pCR (ypT0/is ypN0) in the PD-L1–negative (IC 0) population
  - Event-free survival (EFS), defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause, whichever occurs first, in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
  - DFS, defined as the time from surgery to the first documented disease recurrence or death from any cause, whichever occurs first, in all patients who undergo surgery and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
  - OS, defined as the time from randomization to death from any cause in all patients and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- To evaluate patient-reported outcomes (PROs) of function (role, physical) and health-related quality of life (HRQoL) associated with atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30), on the basis of the following endpoint:
  - Mean and mean changes from baseline score in function (role, physical) and global health status (GHS)/HRQoL by assessment timepoint, and between treatment arms as assessed by the functional and GHS/HRQoL scales of the EORTC QLQ-C30

2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are as follows:

- To evaluate PROs of disease/treatment–related symptoms and emotional, social function associated with atezolizumab + ddAC-PacHP by the EORTC QLQ-C30 on the basis of the following endpoint:
  - Mean and mean changes from baseline score in disease/treatment–related symptoms and emotional, social function by assessment timepoint and between treatment arms as assessed by all symptom items/scales and the emotional, social function scales of the EORTC QLQ-C30
- To evaluate any treatment burden patients may experience associated with the addition of atezolizumab to ddAC-PacHP compared with placebo + ddAC-PacHP, as measured by a single item (GP5: "I am bothered by side effects of treatment") from the physical well-being subscale of the Functional Assessment of Cancer

Therapy−General (FACT-G) quality-of-life instrument on the basis of the following endpoint:

  - 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 EuroQol 5 Dimension, 5-Level (EQ-5D-5L) questionnaire to generate utility scores for use in economic models for reimbursement on the basis of the following endpoint:

  - Utility scores of the EQ-5D-5L questionnaire

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in the neoadjuvant setting and the safety of atezolizumab combined with trastuzumab + pertuzumab (or combined with trastuzumab emtansine) compared with placebo combined with trastuzumab + pertuzumab (or combined with trastuzumab emtansine) in the adjuvant EBC setting on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of atezolizumab, pertuzumab, and trastuzumab when given in combination and of atezolizumab and trastuzumab emtansine when given in combination on the basis of the following endpoints:

- Peak and trough (maximum serum concentration observed [C_{max}] and minimum serum concentration under steady-state conditions within a dosing interval [C_{min}]) of atezolizumab concentrations in serum at specified timepoints
- Trough concentration for pertuzumab and trastuzumab in serum at specified timepoints
- Peak and trough concentration for trastuzumab emtansine in serum at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab, trastuzumab, pertuzumab, and trastuzumab emtansine on the basis of the following endpoints:

- Incidence of treatment-emergent anti-drug antibodies (ADAs) to atezolizumab and its impact on pharmacokinetics, efficacy, and safety

- Incidence of treatment-emergent ADAs to trastuzumab, pertuzumab, and trastuzumab emtansine

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVES

The secondary biomarker objectives for this study are as follows:

- To evaluate pCR (ypT0/is ypN0), EFS, DFS, and OS based upon PIK3CA mutation status

The exploratory biomarker objectives for this study are as follows:

- To evaluate pCR (ypT0/is ypN0) based upon stromal TIL infiltration level
- To evaluate pCR (ypT0/is ypN0) based upon immune gene expression level
- To identify biomarkers and/or changes in biomarkers that are predictive of response to atezolizumab + ddAC-PacHP (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to atezolizumab + ddAC-PacHP, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of atezolizumab + ddAC-PacHP activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:
  - Relationship between biomarkers (or changes in biomarkers) in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- To evaluate biomarkers in association with EFS, DFS, and OS
- To evaluate post-surgical circulating-tumor DNA (ctDNA) with outcome
- To evaluate ctDNA on-treatment changes associated with atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP and to evaluate its association with EFS, DFS, and OS

3. STUDY DESIGN

3.1 DISCONTINUATION OF EXPERIMENTAL TREATMENT AND UNBLINDING AT STUDY LEVEL

On 26 January 2021, the iDMC met and conducted a review of unblinded safety and efficacy data. Following their review of the data, the iDMC recommended to stop randomized treatment assignment with atezolizumab or placebo. Study treatment without atezolizumab/placebo should be continued through the completion of the

adjuvant treatment phase. On 3 February 2021, the Sponsor issued an "Urgent Safety Measure Dear Investigator Letter" (USM DIL) communicating the request to stop treatment with atezolizumab or placebo and informed about the unblinding of the study.

The addition of atezolizumab did not result in an increase in the pCR rate compared with the control arm both in the ITT and the PD-L1–positive population. There were four Grade 5 adverse events in the atezolizumab arm, which occurred in the neoadjuvant phase. The iDMC commented that the difference in death between the two arms was not significant but in the margin of significance. Considering that the majority of the patients had undergone surgery, their recommendation was to stop the atezolizumab/placebo treatment administration from an ethical perspective.

3.1.1 Implications of Unblinding on Study Design and Assessments

Following the discontinuation of atezolizumab or placebo, patients should continue all other study drugs without atezolizumab or placebo and follow study assessments and follow-up assessments as described in Appendix 1. Following the implementation of Protocol, Version 5, the PK and ADA sample collection for atezolizumab, trastuzumab, and pertuzumab (or trastuzumab emtansine) is only required at the treatment discontinuation visit (Appendix 2).

The study was unblinded on 5 February 2021 and the unblinding date will be used as the clinical cutoff date for the primary analysis. As per Statistical Analysis Plan (SAP), patients with missing pCR assessment will be counted as not achieving pCR in the analysis; this includes patients who have not yet undergone surgery and pCR assessment due to the early unblinding of the study. Patients who are still in the neoadjuvant phase of the study at the time of unblinding should continue their study treatment without atezolizumab or placebo and undergo surgery and pathological assessment as per study protocol followed by the adjuvant study phase with study treatment excluding atezolizumab or placebo.

3.2 DESCRIPTION OF THE STUDY PRIOR TO STOPPING BLINDED TREATMENT

3.2.1 Overview of Study Design

This is a global Phase III, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PacHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3, M0).

Patients who have histologically confirmed invasive HER2-positive breast cancer with a primary tumor size >2 cm by any radiologic measurement and who are node positive (node positivity pathologically confirmed by fine-needle aspiration or core-needle biopsy) are eligible. Axillary surgery (including sentinel-node biopsy) prior to neoadjuvant treatment is prohibited. HER2 positivity of the primary breast tumor will be confirmed by

a central laboratory (see Appendix 7 and Appendix 8). Patients whose tumors are not centrally confirmed to be HER2-positive will not be eligible. Patients whose tumor tissue is not evaluable for PD-L1 by central laboratory will not be eligible. Patients who do not initially meet eligibility criteria may be re-screened once.

Figure 1 presents an overview of the study design. The schedules of activities are provided in Appendix 1, Appendix 2, and Appendix 3.

Figure 1 Study Schema

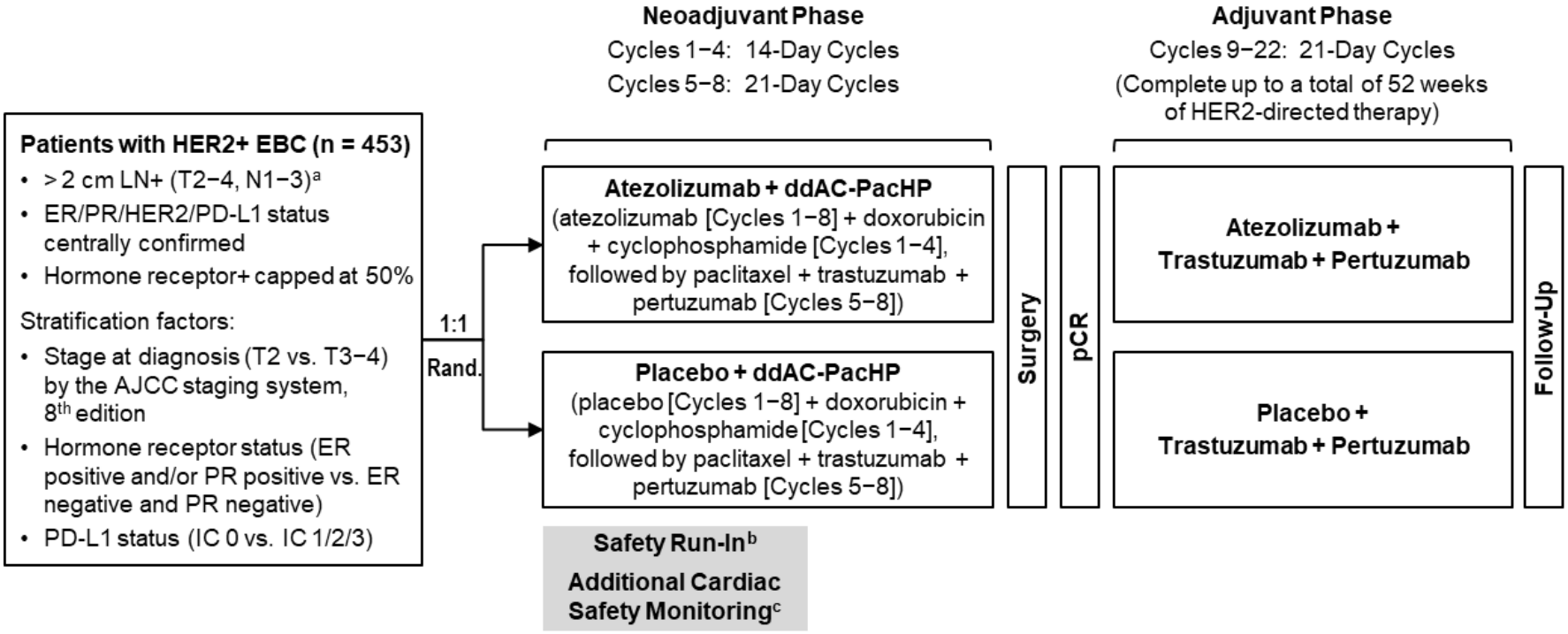
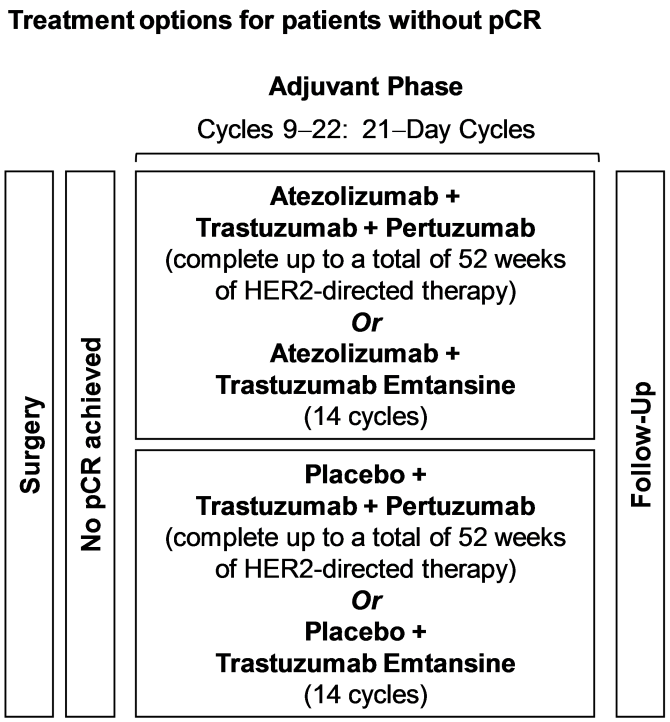


Figure 1 Study Schema (cont.)



Notes: Following the receipt of the Urgent Safety Measure Dear Investigator Letter (USM DIL) dated 3 February 2021, patients will no longer receive atezolizumab or placebo.

If trastuzumab emtansine is discontinued for toxicity not considered related to the trastuzumab component of the drug, treatment can be switched to trastuzumab and pertuzumab with atezolizumab/placebo to complete a total of 1 year of HER2-targeted therapy. Patients discontinued from trastuzumab emtansine for pneumonitis may not switch study treatment to trastuzumab and pertuzumab and have to discontinue all study treatment.

Figure 1 Study Schema (cont.)

ddAC-PacHP = dose-dense anthracycline (doxorubicin) + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; EBC = early breast cancer; ECHO = echocardiogram; ER = estrogen receptor; HER2 = human epidermal growth factor 2; LN = lymph node; MUGA = multiple-gated acquisition (scan); pCR = pathologic complete response; PR = progesterone receptor; Rand = randomization.

[a] LN+ determined through imaging and biopsy. Ulcerating or inflammatory breast (e.g., erythema and/or dermal involvement, and/or pathologic detection of tumor cells in dermal lymphatics) cancer are excluded.

[b] A real-time structured safety assessment of the first 12 patients enrolled (approximately 6 patients per arm) will be performed by the Sponsor and iDMC (without stopping accrual) after the first 12 patients have completed 4 cycles of atezolizumab/placebo + ddAC chemotherapy and 2 cycles of atezolizumab/placebo + PacHP chemotherapy.

[c] The first 26 patients enrolled (approximately 13 patients per arm) will undergo additional cardiac safety monitoring, including an additional ECHO or MUGA scan after the second dose of ddAC chemotherapy, as part of a cardiac safety cohort.

Patients who have consented and are eligible will be randomized in a 1:1 ratio to receive either atezolizumab or placebo administered IV in combination with the current standard neoadjuvant therapy for early HER2-positive breast cancer.

Randomization will be stratified by the following factors:

- Stage at diagnosis (T2; T3 or 4) as determined by the AJCC staging system, 8th edition (specifically according to the Anatomic Stage Group rules)
- Hormone receptor status (ER positive and/or PgR positive; ER negative and PgR negative)
  - Hormone receptor–positive status will be capped at 50%.
- PD-L1 status (IC 0; IC 1/2/3)

Study treatment administration should begin within 7 days after randomization.

During the neoadjuvant phase (i.e., prior to surgery; Cycles 1–8), all patients will receive:

- Atezolizumab or placebo 840 mg IV every 2 weeks (Q2W) for 4 cycles (Cycles 1–4)
- ddAC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 IV) given with granulocyte colony–stimulating factor (G-CSF), granulocyte macrophage colony–stimulating factor, or pegylated granulocyte colony–stimulating factor support in accordance to local guidelines Q2W for 4 cycles (Cycles 1–4)

Followed by:

- Atezolizumab or placebo 1200 mg IV every 3 weeks (Q3W) for 4 cycles (Cycles 5–8)
- Paclitaxel 80 mg/m^2 IV every week (QW) for 4 cycles (Cycles 5–8)
- Trastuzumab 6 mg/kg IV (with an initial 8-mg/kg IV loading dose) Q3W for 4 cycles (Cycles 5–8)
- Pertuzumab 420 mg IV (with an initial 840-mg IV loading dose) Q3W for 4 cycles (Cycles 5–8)

A cycle will be considered missed during the neoadjuvant phase if the subsequent cycle cannot be administered within 28 days of the last dose for Cycles 1–4 or within 42 days of the last dose for Cycles 5–8. In this situation, make-up treatment of missed cycles of chemotherapies is permitted post-surgery (see Appendix 11) prior to the adjuvant phase (described below).

During the adjuvant phase (i.e., post-surgery; Cycles 9–22), the following study treatments will be continued Q3W to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting:

- Atezolizumab/placebo 1200 mg IV Q3W
- Trastuzumab 6 mg/kg IV (with an initial 8-mg/kg IV loading dose) Q3W

- Pertuzumab 420 mg IV (with an initial 840-mg IV loading dose) Q3W

Patients who do not achieve a pCR as defined in the protocol (i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition) have the option of receiving adjuvant treatment as outlined above or alternatively:

- Atezolizumab or placebo as per initial treatment assignment 1200 mg IV Q3W combined with trastuzumab emtansine 3.6 mg/kg IV Q3W

Treatment assignment will not be unblinded following pCR evaluation. The treatment decision for patients who do not achieve a pCR after neoadjuvant therapy is per investigator discretion.

Atezolizumab/placebo + trastuzumab + pertuzumab will be given to complete 52 weeks of HER2-directed therapy (i.e., a maximum of 18 cycles of HER2-directed therapy). Adjuvant atezolizumab/placebo + trastuzumab emtansine will be given for 14 cycles. If trastuzumab emtansine is discontinued for toxicity not considered related to the trastuzumab component of the drug, treatment can be switched to trastuzumab and pertuzumab with atezolizumab/placebo to complete a total of 1 year of HER2-targeted therapy.

Patients who discontinue neoadjuvant therapy early as a result of disease progression must be discontinued from all study treatment and will be managed as per local practice. Any patient who receives non-protocol therapy prior to surgery will be discontinued from study treatment and will be managed as per local practice; these patients will remain in the follow-up phase of the study. For patients who do not achieve pCR, it is recommended to continue on study treatment with the option to receive atezolizumab/placebo + HP or atezolizumab/placebo + trastuzumab emtansine on the basis of a benefit–risk assessment for the individual patient. Alternatively, as per investigator discretion, local clinical guidelines for management of non-pCR patients may be followed; the patient will remain in the follow-up phase of the study.

Patients who discontinue one or more of the study treatment components due to toxicity should not be automatically withdrawn from all study treatments. Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Table 2, Table 3, Table 4, Appendix 11, and Appendix 12.

Patients who discontinue early from all components of the pre- or post-operative study treatment should remain in the follow-up phase of the study. Patients who discontinue prematurely from the study will not be replaced.

The primary efficacy endpoint (pCR; ypT0/is ypN0) will be established via local review following completion of neoadjuvant therapy and surgery. In line with pCR guidance from the FDA (2014), pathologists who review study specimens will conduct review of

study specimens in a blinded manner. Pathologists must utilize the evaluations and assessments outlined in the study pathology manual. Surgery should be performed at least 14 days after the last dose of neoadjuvant study treatment but no later than 6 weeks after the last infusion. Platelet counts should be checked prior to surgery and should be $\geq$75,000 cells/μL. Patients must undergo full axillary lymph node dissection at the time of definitive surgery. Sentinel lymph node procedure alone is not permitted. If surgically feasible, it is recommended that at least 10 lymph nodes are removed for pathologic examination. For sentinel nodes involving the internal mammary chain, refer to local, national, or international guidelines. Level III axillary dissections should be performed for patients with gross disease in the Level II nodes. The first dose of postoperative treatment should not start until 2 weeks after surgery but should be administered within 45 days of surgery. Postoperative patient management for those in either treatment arm may include radiotherapy and hormonal therapy as clinically indicated and in accordance with standard local clinical practice (see Section 4.4.1).

An iDMC will evaluate safety data and study conduct on a regular basis during the study until the analysis of the primary endpoint of pCR, after which iDMC review of the study data will be discontinued. An administrative interim analysis of efficacy will also take place once 227 patients have been enrolled, completed neoadjuvant treatment, and undergone surgery. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles, responsibilities, and timing of iDMC meetings. To assess the potential cardiac toxicity of the combination of anthracyclines and atezolizumab, the iDMC will review data from a cardiac safety cohort involving additional cardiac monitoring in the first 26 patients enrolled (approximately 13 patients in the control arm and approximately 13 patients in the atezolizumab arm) after all 26 patients have completed or have discontinued the neoadjuvant portion of the study.

A real-time safety assessment of the first 12 patients enrolled (approximately 6 patients in the control arm and approximately 6 patients in the atezolizumab arm) will be conducted without stopping accrual. This safety evaluation by the Sponsor of blinded data and the iDMC of unblinded data will be conducted after the first 12 patients have completed 6 cycles of neoadjuvant therapy (4 cycles of atezolizumab/placebo + ddAC and 2 cycles of atezolizumab/placebo + PacHP).

Following completion of study treatment and surgery, all patients will continue to be followed for efficacy, safety, and PRO objectives until the end of the study. No interim efficacy analyses for early stopping are planned, although an administrative interim analysis of efficacy is planned (see Section 3.2.2). Safety assessments will include the occurrence and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Tumor tissue will also be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator, at the time of disease recurrence. These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab.

3.2.2 Independent Data Monitoring Committee

An iDMC will evaluate safety data on a regular basis during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles, responsibilities and timing of iDMC meetings.

Unblinded safety data will be reviewed on a regular basis by the iDMC. To assess the potential toxicity of the combination, the iDMC, including a cardiologist, will review data from a cardiac safety cohort in the first 26 patients enrolled (approximately 13 patients in the control arm and approximately 13 patients in the atezolizumab arm) after all 26 patients have completed or have discontinued the neoadjuvant portion of the study. Subsequent safety reviews will occur periodically during the study, as defined in the iDMC Charter, until analysis of the primary endpoint (refer to the iDMC Charter).

An administrative interim efficacy analysis is planned once 227 patients have been enrolled, completed neoadjuvant treatment and undergone surgery, with the results reviewed by the iDMC.

All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC).

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

3.3 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 36 months after the last patient is enrolled in the global study. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 54 months, assuming a recruitment period of approximately 18 months, and follow-up for 36 months from the date of enrollment of the last patient in the study. The Sponsor may decide to terminate the study at any time.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 840 mg Q2W by IV infusion in combination with ddAC chemotherapy to align with the chemotherapy schedule (Cycles 1–4). The atezolizumab dosing regimen will be switched to 1200 mg Q3W for subsequent cycles.

The average atezolizumab exposure following the 840 mg Q2W dosage (approved by the FDA in March 2019) is expected to be similar to that of 1200 mg Q3W (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies and available clinical PK, efficacy, and safety data (Deng et al.2016; refer to the to the Atezolizumab Investigator's Brochure for details).

Based on the understanding of population-PK variability and atezolizumab concentration–tumor dynamic relationship, 840 mg Q2W and 1200 mg Q3W are expected to have comparable efficacy and safety profiles.

3.4.2 Rationale for Chemotherapy Choice and Schedule

The backbone chemotherapy regimens (anthracycline followed by taxane) used with HER2-directed therapy in the neoadjuvant part of this study are based on published data, routine clinical usage, as well as established clinical practice guidelines (e.g., Senkus et al. 2013; Gradishar et al 2017; Curigliano et al. 2017) for patients with high-risk, HER2-positive EBC, in combination with pertuzumab and trastuzumab. The doses of chemotherapy in this trial are all consistent with the prescribing information for each agent.

NCCN-preferred neoadjuvant/adjuvant regimens for HER2-positive EBC are AC or ddAC followed by QW paclitaxel with trastuzumab given concurrently with paclitaxel. As per NCCN guidelines, pertuzumab can be added to trastuzumab-containing regimens including AC-paclitaxel (various schedules) for patients with HER2-positive EBC and a tumor size ≥ 2 cm in diameter or node positive. The St. Gallen Guidelines also recommended dual anti-HER2 therapy with pertuzumab and trastuzumab and chemotherapy in the neoadjuvant setting for high-risk, HER2-positive patients. The recommended chemotherapy regimen is anthracycline followed by taxane with concurrent HER2 therapy (Curigliano et al. 2017).

Citron et al. (2003) compared standard Q3W and accelerated Q2W schedules of concurrent doxorubicin and cyclophosphamide followed by paclitaxel, or sequential doxorubicin, paclitaxel, and cyclophosphamide. There was a significant improvement in OS with dose-dense therapy (risk ratio $= 0.69$, $p = 0.013$), with 3-year OS of 92% in the dose-dense arms and 90% in the Q3W arms. The SWOG S0221 study has shown that patients treated with weekly paclitaxel demonstrated equivalent efficacy to those treated with Q2W paclitaxel (Budd et al. 2017).

Combining dose-dense AC followed by paclitaxel and HER2-targeted therapy appears to be safe from a cardiac point of view, and toxicity does not seem to be increased in relation to previous non–dose-dense HER2 clinical trials (Dang et al. 2008;

Dang et al. 2010; Hudis et al. 2014). The BERENICE study explored the regimen that is used in the current study, namely ddAC followed by paclitaxel QW; pertuzumab and trastuzumab were given concurrently with the taxane. The regimen was active, with high tpCR rate. Cardiac and general safety of this regimen was as expected and was consistent with the known pertuzumab, trastuzumab, and chemotherapy safety profiles (Swain et al. 2018).

3.4.3 Rationale for Patient Population

This study will enroll patients with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3). Patients are required to have histologically confirmed invasive HER2-positive breast cancer with a primary tumor size >2 cm and node-positive disease (node positivity pathologically confirmed by fine-needle aspiration or core-needle biopsy). HER2 status will be centrally confirmed. Based on observations in Study WO30085 in patients with HER2-positive advanced breast cancer, the expected proportion of PD-L1–positive (IC 1/2/3) patients in Study BO40747 is approximately 40% (using the Ventana anti–PD-L1 SP142 immunohistochemistry assay; Emens et al. 2018).

Breast cancers over-expressing HER2 are the most aggressive type of breast cancers. Although current therapies have significantly improved patient outcomes in these patients, there are still those who remain at high risk for recurrence and who have poor long-term outcomes. These patients are largely identified using clinical parameters, including tumor size >2 cm and positive nodal status. In NEOSPHERE, a study in which enrolled patients were required to have tumors >2 cm, the 5-year DFS rate in patients treated with neoadjuvant trastuzumab and pertuzumab with standard chemotherapy was 84% (Gianni et al. 2016). Data from the APHINITY study have demonstrated high invasive DFS rates at 3 years (94.1%) and 4 years (92.3%) with adjuvant trastuzumab and pertuzumab plus chemotherapy (von Minckwitz et al. 2017). However, in patients with node-positive disease, these values were numerically lower at both 3 years (92%) and 4 years (89.9%). Patients with node-positive disease fared worse compared with the ITT population when treated with adjuvant chemotherapy+trastuzumab and pertuzumab in the APHINITY clinical trial (invasive DFS HR 0.77 vs. 0.81).

The patient population for this study was selected to target those patients who are at highest risk for recurrence and where the potential for cancer immunotherapy to improve long-term patient outcomes can have the greatest impact.

3.4.4 Rationale for Control Group and Combination with Atezolizumab

The control group for this study is current SOC for high-risk patients with HER2-positive EBC. The combination of chemotherapy with trastuzumab and pertuzumab is approved for use in the neoadjuvant setting and adjuvant continuation of this combination therapy is currently approved in the United States and European Union. The NCCN guidelines recommend the usage of AC-taxane-HP as pre-operative/adjuvant therapy in patients

with ≥T2 or ≥N1 HER2-positive, early-stage breast cancer (Curigliano et al. 2017; Association of Gynecologic Oncology [AGO] Guidelines 2018; Denduluri et al. 2018; NCCN Guidelines Version 4.2017 [Gradishar et al. 2018]). Although guidelines have yet to be updated with recent APHINITY data, the 2015 ESMO Breast Cancer Clinical Practice Guidelines also consider the usage of trastuzumab+pertuzumab combination with chemotherapy as an acceptable option as neoadjuvant therapy (Senkus et al. 2013).

It is hypothesized that an important mechanism of action of therapeutic antibodies such as trastuzumab and pertuzumab is to induce cellular immunity via interactions with the Fc fragment of the molecule and/or destroy malignant cells resulting in release of tumor antigens for uptake by antigen-presenting cells, which in turn upregulate immune effector cells. The combination of these agents with an anti−PD-L1 inhibitor might help to further enhance anti-tumor immune responses.

Nonclinical models provide support for this hypothesis. It has been demonstrated that the addition of PD-1:PD-L1 blockade improves the therapeutic activity of an anti-HER2 monoclonal antibody in a murine model of HER2-positive breast cancer (Stagg et al. 2011). This is supported by additional nonclinical data in murine models that show the combination of atezolizumab with trastuzumab, pertuzumab, and chemotherapy results in increased tumor immune infiltrate compared with any of the agents alone or in combinations that do not include atezolizumab (data on file). These findings suggest that anti−PD-L1 immunostimulatory approaches may further capitalize upon the immune-mediated effects of therapeutic antibodies such as trastuzumab and pertuzumab.

3.4.5 Rationale for Trastuzumab Emtansine in Combination with Atezolizumab as Adjuvant Treatment Option

Results from Study BO27938 (Katherine) demonstrated a significant reduction in the risk of recurrence of invasive breast cancer or death in patients with HER2-positive early breast cancer with residual invasive disease after completion of neoadjuvant therapy who were treated with adjuvant trastuzumab emtansine compared with those treated with adjuvant trastuzumab (HR=0.50; 95% CI, 0.39−0.64; p<0.001; von Minckwitz et al. 2019). These data resulted in a recent update of the NCCN guidelines that recommend trastuzumab emtansine for patients with residual disease for 14 cycles. The guidelines further recommend to switch treatment to trastuzumab±pertuzumab in patients who have to discontinue trastuzumab emtansine for toxicity to complete 1 year of HER2-targeted therapy (NCCN 2019).

At the discretion of the investigator, the adjuvant treatment options offered in the study (BO40747) for patients not achieving pCR are trastuzumab emtansine in combination with atezolizumab/placebo as assigned at randomization without unblinding of the treatment arms, or atezolizumab/placebo+trastuzumab+pertuzumab. This study (BO40747) will explore trastuzumab emtansine in combination with atezolizumab in

patients with non-pCR with exposure in a limited number of patients. Based on the assumption that 227 patients will be randomized to the experimental arm, an estimated drop-out rate of 10%, and an estimated pCR rate of 80% in the experimental arm, approximately 41 patients will be eligible to receive atezolizumab + trastuzumab emtansine based on their non-pCR status. Similarly, 82 patients in the control arm are estimated to be eligible to receive placebo + trastuzumab emtansine based on their non-pCR status.

3.4.6 Rationale for Pathologic Complete Response as Primary Endpoint

The co-primary objective of this study is to evaluate the efficacy of atezolizumab + ddAC-PacHP compared with placebo + ddAC-PacHP in patients with newly diagnosed HER2-positive breast cancer in the ITT and PD-L1–positive patient populations. Efficacy will be assessed using pCR.

pCR was selected as the primary efficacy endpoint because it is a validated, meaningful measure of response to therapy, and on the basis of data from several analyses and clinical trials and meta-analyses, there is an association between the pCR status of a patient and long-term outcomes (Liedtke et al. 2008; von Minckwitz et al. 2012; Cortazar et al. 2014). More recently, data from the I-SPY 2 trial have shown that achieving pCR is a strong predictor of EFS and distant recurrence-free survival, EFS HR 0.21 [95% CI: 0.05 to 0.85]; DDFS HR 0.22 [95% CI: 0.08 to 0.70] in patients with HER2-positive breast cancer (Tripathy et al. 2017).

pCR will be defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of NAST, in line with the FDA and European Medicines Agency (EMA) guidance for industry on pCR endpoints (i.e., ypT0/Tis ypN0 in the current AJCC staging system).

3.4.7 Rationale for Biomarker Assessments

Published results from several studies suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti–PD-L1 monotherapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016; Schmid et al. 2018). Therefore, given the mode of action of atezolizumab, PD-L1 is considered a potential candidate to predict response to treatment. However, emerging data on the basis of studies targeting the PD-1/PD-L1 pathway showed that the results are complex and ambiguous. Contributing factors are PD-L1 variability between different assays, status of the biopsy, and the dynamic expression of PD-L1. Interestingly, in melanoma, the predictive nature of PD-L1 expression seems to depend on whether the disease is early stage or metastatic. In resected high-risk Stage III melanoma, significantly longer recurrence-free survival was observed with adjuvant pembrolizumab compared with placebo in the ITT population. Pembrolizumab was similarly effective in patients with PD-L1–positive and

PD-L1–negative tumors suggesting that the benefit of anti–PD-1 treatment is not dependent on PD-L1 expression in an early disease setting (Eggermont et al. 2018). In contrast, advanced melanoma patients treated with pembrolizumab in the metastatic setting experienced longer PFS and OS when their tumors were PD-L1–positive compared with patients whose tumors were PD-L1–negative suggesting a predictive role of PD-L1 in this setting (Daud AI et al. 2016). On the basis of these findings, it is hypothesized that the predictive value of PD-L1 expression for atezolizumab may differ between early versus metastatic disease. Given the current uncertainty as to whether cancer immunotherapy can provide benefits in unselected versus PD-L1–selected early breast cancer, this study (BO40747) will enroll an all-comer population but will test efficacy in the ITT and PD-L1–positive patient populations and stratify randomization on the basis of PD-L1 status.

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 (IC 0 vs. IC 1/2/3) as assessed by immunohistochemistry (IHC).

Other immune markers of interest are TILs. In HER2-positive breast cancer, increased TIL concentrations have shown an association with increased frequency of response to neoadjuvant therapy and longer survival (Loi et al. 2014; Salgado et al. 2015a, 2015b; Denkert et al. 2018; Ignatiadis et al. 2018). Not all data have shown consistent results (Bianchini et al. 2015). A standardized methodology for evaluating TILs has been established and will be applied to tissue samples in this study to understand the role of TILs in clinical benefit of the combination of atezolizumab and ddAC-PacHP (Salgado et al. 2015a, 2015b). In the PANACEA study in patients with HER2-positive metastatic breast cancer treated with trastuzumab and pembrolizumab, the subgroup of patients with PD-L1–positive tumor status and having 5% or more of TILs present in the metastatic tumor achieved an objective response rate of 39%, while no objective responses were observed in the PD-L1–negative cohort (Loi et al. 2016).

Other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of the combination of atezolizumab and ddAC-PacHP, long-term benefit, tumor immunobiology (e.g., TILs, CD8 expression), mechanisms of resistance, or tumor type, may be analyzed. In addition, phosphatase and tensin homolog may be performed.

Differences in pCR rates and in long-term outcomes between patients with HER2-positive breast cancer with hormone receptor–positive disease and hormone receptor–negative disease have been reported in several Phase II/III studies, showing lower pCR rates for patients with hormone receptor–positive compared with hormone receptor–negative disease with pCR rates varying from 15% to 30% (Gianni et al. 2012; Untch et al. 2016; Zhang and Hurvitz 2016; Swain et al. 2018).

In this study, baseline tumor specimens will be tested for ER and PgR status and randomization will be stratified based upon centrally confirmed hormone receptor status. Another biomarker of interest is PIK3CA mutation. Lower pCR rates in patients carrying a PIK3CA mutation were observed in the neoadjuvant setting across several trials in HER2-positive breast cancer (Schneeweis et al. 2013; Majewski et al. 2015; Loibl et al. 2016). Therefore, PIK3CA mutations will also be assessed retrospectively in this study.

In addition to baseline tumor collection, tumor tissue will also be collected by biopsy at the time of disease recurrence if deemed clinically feasible by the investigator to enable analysis of tumor tissue biomarkers related to resistance, disease progression, clinical benefit of the combination of atezolizumab and ddAC-PacHP, and long-term efficacy.

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 and lymphocyte subpopulations, and ctDNA may provide evidence of biologic activity of the combination of atezolizumab and ddAC-PacHP and of their association with long-term efficacy outcomes. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from the combination of atezolizumab and ddAC-PacHP. Exploratory biomarkers will also be tested for association with long-term efficacy.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

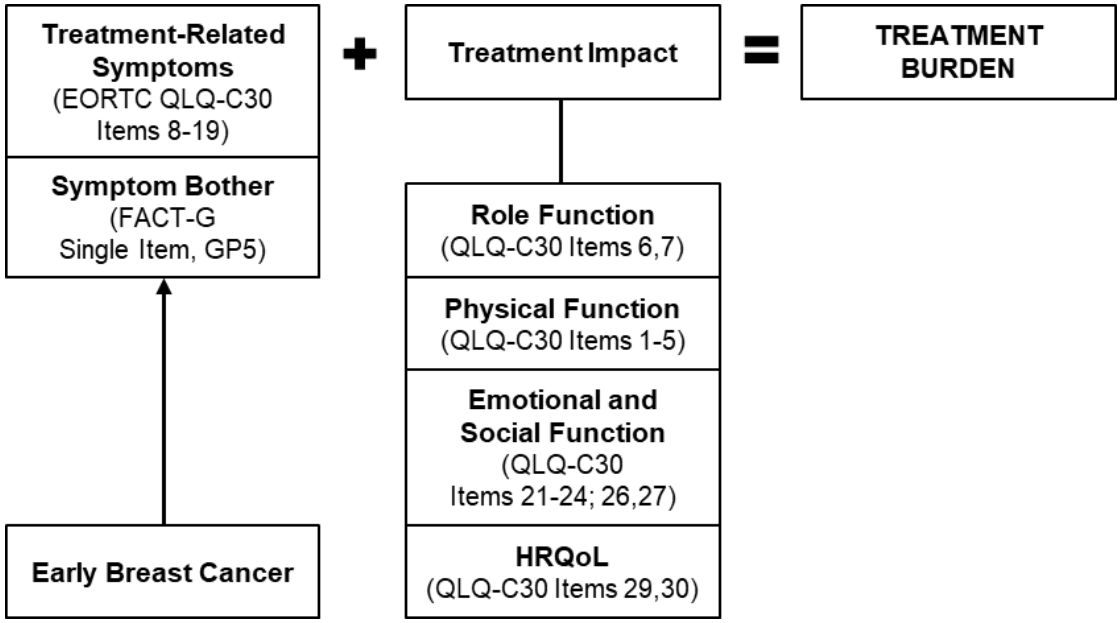
3.4.8 Rationale for Patient-Reported Outcome Assessments

EBC is largely asymptomatic, with the majority of newly diagnosed patients exhibiting no disease-specific, discernable symptoms (Barrett 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 helping inform 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). Therefore, it is 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, 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 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 GHS/HRQoL, functional, and disease/treatment–related symptom items and scales of the EORTC QLQ-C30 (see Appendix 4) and the treatment bother item GP5 from the FACT-G (see Appendix 5) quality-of-life instrument will all be used to assess patients' treatment burden (see Figure 2).

Figure 2 Documenting Treatment Burden in Patients with Early Breast Cancer



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 to support and inform the benefit–risk assessment of atezolizumab therapy (Cella 1997; Fayers et al. 2001).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 453 patients with cT 2–4, cN1–3, cM0 HER2-positive breast cancer (tumor >2 cm and lymph node positive) will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Confirmed diagnosis of HER2-positive breast cancer, and hormonal and PD-L1 status, as documented through central testing of a representative tumor tissue specimen, is required.
  - A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted prior to study enrollment. Any deviation of the material requirements (see Appendix 3) are only allowed after Sponsor's approval has been obtained.
  - HER2-positive status will be determined on the basis of pretreatment breast biopsy material and defined as an IHC score of 3+ or positive by in situ hybridization (ISH; see Appendix 3 and Appendix 7) prospectively assessed by a central laboratory prior to study enrollment. ISH positivity is defined as a ratio of ≥2 for the number of HER2 gene copies to the number of signals for chromosome 17 copies. A central laboratory will perform both IHC and ISH assays; however, only one positive result is required for eligibility.
  - PD-L1 status through measurement of IHC will be used for stratification. The maximum PD-L1 score assessed among samples submitted for eligibility will be used as the PD-L1 score for the patient.
  - ER/PgR status will be determined centrally based on pretreatment breast biopsy material according to the American Society of Clinical Oncology (ASCO) and the College of American Pathologists guidelines (Hammond et al. 2010).
- Primary breast tumor size of >2 cm by any radiographic measurement (see Section 4.5.5 for additional details)
- Stage at presentation: T2–T4, N1–N3, M0 as determined by AJCC staging system, 8th edition (specifically in accordance with Anatomic Stage group rules)
- Pathologic confirmation of nodal involvement with malignancy must be determined by fine-needle aspiration or core-needle biopsy. Surgical excision of lymph nodes (e.g., sentinel lymph node biopsy and axillary lymph node biopsy) is not permitted.
- Patients with multifocal tumors (more than one mass confined to the same quadrant as the primary tumor) are eligible provided at least one focus is sampled and

centrally confirmed as HER2-positive (see Appendix 3 for tissue sample requirements).

- Patients with multicentric tumors (multiple tumors involving more than one quadrant) are eligible provided all discrete lesions are sampled and centrally confirmed as HER2 positive (see Appendix 3 for tissue sample requirements).
  - In patients with multifocal or multicentric breast cancer, the largest lesion should be measured to determine T stage.
- Patient agreement to undergo appropriate surgical management, including axillary lymph node surgery and partial or total mastectomy, after completion of neoadjuvant treatment
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Baseline LVEF $\geq 55\%$ measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500 cells/μL) without G-CSF support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500 cells/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000 cells/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)

    Patients may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN)
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN within 14 days prior to initiation of study treatment
  - For patients receiving therapeutic anticoagulation:

    INR or aPTT within therapeutic limits for at least 1 week immediately prior to initiation of study treatment

    Stable anticoagulant regimen and stable INR during the 14 days immediately preceding initiation of study treatment
- 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.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, 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 5 months after the final dose of atezolizumab/placebo, 6 months after the final dose of doxorubicin, 12 months after the final dose of cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab. pertuzumab, or trastuzumab emtansine, whichever occurs last. Women must refrain from donating eggs during this same period.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, copper intrauterine devices, hormonal contraceptives that inhibit ovulation, and hormone-releasing intrauterine devices in women with hormone receptor-negative tumors only; the use of hormonal contraceptives and hormone releasing intrauterine devices are prohibited in women with hormone receptor–positive tumors.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 final dose of doxorubicin and/or cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last. Men must refrain from donating sperm during this same period. Male patients are encouraged to seek advice

regarding cryoconservation of sperm prior to commencing study treatment because of the possibility of infertility with chemotherapy.

- With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of doxorubicin and/or cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last to avoid exposing the embryo.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

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

- Prior history of invasive breast cancer
- Stage IV (metastatic) breast cancer
  - Baseline tumor staging determination should be performed in alignment with AJCC staging system, 8th edition (specifically in accordance with Anatomic Stage group rules).
- Patients with synchronous bilateral invasive breast cancer
- Patients with hormone receptor−positive disease (estrogen receptor−positive and/or progesterone receptor−positive) will be excluded once approximately 227 patients (50% of the total target sample size) with hormone receptor−positive disease have been enrolled.
- Prior systemic therapy for treatment of breast cancer
- Previous therapy with anthracyclines or taxanes for any malignancy
- Ulcerating or inflammatory breast cancer (e.g., erythema and/or dermal involvement, and/or pathologic detection of tumor cells in dermal lymphatics)
- Undergone incisional and/or excisional biopsy of primary tumor and/or axillary lymph nodes
- Sentinel lymph node procedure or axillary lymph node dissection prior to initiation of neoadjuvant therapy
- History of other malignancy within 5 years prior to screening, with the exception of those patients who have a negligible risk of metastasis or death (e.g., 5-year OS of $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Cardiopulmonary dysfunction as defined by any of the following prior to randomization:
  - History of congestive heart failure of any classification

- 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 $>$180 mmHg and/or diastolic blood pressure $>$100 mmHg)
- Evidence of transmural infarction on ECG
- Requirement for oxygen therapy
- Dyspnea at rest

- 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 antibody syndrome, granulomatosis $with\ polyangiitis$, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 9 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on a stable dose of thyroid-replacement hormone are eligible for the study.
  - Patients with controlled type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all the following conditions are met:

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

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

    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, or 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.

- Active tuberculosis
- 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 the study
- Severe infection 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 antibiotics within 2 weeks (IV antibiotics) or 5 days (oral antibiotics) prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease [COPD] exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug and may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab/placebo treatment or within 5 months after the final dose of atezolizumab/placebo
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–cytotoxic T lymphocyte-associated protein-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferon and interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - Cyclophosphamide as part of the study treatment
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor approval has been obtained.
  - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to the components of the paclitaxel, cyclophosphamide, or doxorubicin formulations
- Known allergy or hypersensitivity to trastuzumab or pertuzumab formulations
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab/placebo, 6 months after the final dose of doxorubicin, 12 months after the final dose of cyclophosphamide, 6 months after the final dose of paclitaxel, or 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine, whichever occurs last
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.

Exclusions Related to Trastuzumab Emtansine in the Adjuvant Setting

- Patients who achieved pCR defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/is ypN0 in the current AJCC staging system, 8th edition)
- Evidence of clinically evident gross residual or recurrent disease following neoadjuvant therapy and surgery
- Unable to complete surgery with curative intent after conclusion of neoadjuvant systemic therapy
- Patient discontinued treatment with trastuzumab because of toxicity during the neoadjuvant phase of the study.
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, or sclerosis cholangitis
- Patients with current Grade ≥ 2 peripheral neuropathy
- Prior treatment with trastuzumab emtansine
- Serum AST, ALT, and alkaline phosphatase not within $\leq 1.5 \times$ ULN
- Serum total bilirubin not within normal range ($\leq 1.0 \times$ ULN)
  - Except for patients with Gilbert's syndrome, for whom direct bilirubin should be within the normal range.
- Serum creatinine not within $< 1.5 \times$ ULN

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

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.

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 + neoadjuvant ddAC-PacHP or placebo + neoadjuvant ddAC-PacHP. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the categories defined for the following stratification factors at baseline:

- Stage at diagnosis (T2, T3–4)
- Hormone receptor status (ER positive and/or PgR positive; ER negative and PgR negative)
  - Enrollment of patients with hormone receptor–positive disease will be capped at 50%.
- PD-L1 status (IC 0; IC 1/2/3)

Patients should receive their first dose of study treatment on the day of randomization if possible. If treatment is not possible, the first dose should occur no later than 7 days after randomization.

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial (e.g., IxRS service provider and iDMC members).

In general, unblinding of participants during the conduct of the clinical trial is not allowed. If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, investigators are encouraged to consult with the Medical Monitor prior to performing unblinding. If knowledge of treatment assignment is required to help investigators decide whether patients should switch to or start an approved therapy, the investigator will be able to break the treatment code by contacting the IxRS. Investigators are not allowed to break the treatment code to help decide if patients should switch to or start an unapproved therapy (including investigational treatments in other clinical trials) without prior approval by Medical Monitor.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.

On 26 January 2021, the iDMC met and conducted a review of unblinded safety and efficacy data. Following their review of the data, the iDMC recommended to stop randomized treatment assignment with atezolizumab or placebo. The Sponsor accepted the iDMC recommendation and on 3 February 2021, issued a USM DIL communicating the request to stop treatment with atezolizumab or placebo and the unblinding of the study. The Sponsor unblinded the study on 5 February 2021 and subsequently informed sites about treatment assignment of their patients.

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

While PK and ADA samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples will be analyzed for all patients. Postbaseline ADA samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab, trastuzumab, pertuzumab, trastuzumab emtansine, doxorubicin, cyclophosphamide, and paclitaxel. The IMPs required for completion of this study will be provided by the Sponsor where required by local health authority regulations.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab and Placebo

On 3 February 2021, the Sponsor issued a USM DIL communicating the request to stop treatment with atezolizumab or placebo. Therefore, atezolizumab and placebo will no longer be supplied by the Sponsor following this date. The following information reflects the situation prior to the USM DIL.

The atezolizumab Drug Product and placebo will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution; 14 mL of vial content contains approximately 840 mg of atezolizumab.

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

4.3.1.2 Pertuzumab (Perjeta®)

Pertuzumab will be supplied by the Sponsor as a single-use formulation containing 30 mg/mL pertuzumab formulated in 20 mM L-histidine (pH 6.0), 120 mM sucrose, and 0.02% polysorbate-20. Each 20-cc vial contains approximately 420 mg of pertuzumab (14.0 mL/vial). For information on the formulation and handling of pertuzumab, see the pharmacy manual and the Pertuzumab Investigator's Brochure, or the local prescribing information for pertuzumab.

4.3.1.3 Trastuzumab (Herceptin®)

Trastuzumab will be supplied by the Sponsor in vials containing a freeze-dried preparation for parenteral administration. The vial is reconstituted with Sterile Water for Injection and the reconstituted solution contains 21 mg/mL.

For information on the formulation and handling of trastuzumab, see the pharmacy manual and the Trastuzumab Investigator's Brochure, or the local prescribing information for trastuzumab.

4.3.1.4 Trastuzumab Emtansine (Kadcyla®)

Trastuzumab emtansine will be supplied by the Sponsor in vials containing freeze-dried product. The vial is reconstituted with Sterile Water for Injection and the reconstituted solution contains 20 mg/mL.

For information on the formulation and handling of trastuzumab emtansine, see the pharmacy manual and the Trastuzumab Emtansine Investigator’s Brochure, or the local prescribing information for trastuzumab emtansine.

4.3.1.5 Chemotherapy

Doxorubicin, cyclophosphamide, and paclitaxel are administered in accordance with local prescribing information. These drugs will be obtained locally by the investigational sites or will be provided by the Sponsor as per country requirements.

Refer to the respective local prescribing information or other appropriate local reference document for information on the formulation, preparation, administration, contraindications, and patient monitoring.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.2.1 and Figure 1.

All study therapy will be completed following 52 weeks of HER2-directed therapy (neoadjuvant and adjuvant; i.e., a maximum of 18 cycle of HER2-directed therapy). Surgery should be performed at least 14 days after the last dose of neoadjuvant therapy but no later than 6 weeks after the last infusion. Platelet counts should be checked prior to surgery and should be ≥75,000 cells/μL.

The first dose of postoperative treatment should not start until 2 weeks after surgery but should be administered within 45 days of surgery.

Treatment will continue as scheduled or until progression, recurrence of disease, or unmanageable toxicity.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Patients who discontinue one or more of the study treatment components due to toxicity should not be automatically withdrawn from all study treatments.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events and the timing of surgery are provided in Appendix 11 and Appendix 12.

4.3.2.1 Atezolizumab and Placebo

On 3 February 2021, the Sponsor issued a USM DIL communicating the request to stop treatment with atezolizumab or placebo.

During the neoadjuvant phase, atezolizumab/placebo will be administered by IV infusion at a fixed dose of 840 mg on Day 1 of each 14-day cycle during Cycles 1–4, and 1200 mg on Day 1 of each 21-day cycle during Cycles 5–8. During the adjuvant phase (post-operatively), atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (maximum of 22 cycles [neoadjuvant + adjuvant phases]). Atezolizumab/placebo should be administered as the first infusion.

Treatment will continue as scheduled or until disease progression, recurrence of disease, or unmanageable toxicity.

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 10. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Infusions

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

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 12.

No dose modification for atezolizumab is allowed.

4.3.2.2 Pertuzumab (Perjeta®)

Pertuzumab is given as a fixed non–weight-based dose of 840-mg IV loading dose, then 420 mg IV Q3W. Pertuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting (see Figure 1). Atezolizumab/placebo should be administered prior to pertuzumab and trastuzumab. The order of administration of pertuzumab and trastuzumab is according to investigator preference.

The initial dose of pertuzumab will be administered over 60 (±10) minutes, and patients will be observed for a further 60 minutes. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 (±10) minutes, and patients will be observed for a further 30 minutes for infusion-related symptoms such as fever or chills. All infusion-related symptoms must have resolved before trastuzumab or chemotherapy

is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.10 and Appendix 11. No dose reductions are allowed for pertuzumab. If the patient misses a dose of pertuzumab for any cycle and the time between doses is ≥6 weeks, a reloading dose of pertuzumab (840 mg) should be given. Subsequent maintenance pertuzumab (420 mg) will then be given Q3W, starting 3 weeks later.

If the interval between the first dose of adjuvant pertuzumab and the last dose of neoadjuvant pertuzumab is 6 weeks or more, a reloading dose of 840 mg of pertuzumab is required.

4.3.2.3 Trastuzumab (Herceptin®)

Trastuzumab is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. Trastuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting (see Figure 1). Atezolizumab/placebo should be administered prior to pertuzumab and trastuzumab. The order of administration of pertuzumab and trastuzumab is according to investigator preference.

Weight should be recorded during screening and on Day 1 of each cycle for all patients. The baseline weight for a patient will be that measured on Cycle 1, Day 1. The amount of trastuzumab to be administered must be recalculated if the patient's body weight has changed by >10% (increased or decreased) from the Cycle 1, Day 1 weight. The amount of trastuzumab administered is calculated according to the patient's actual body weight, with no upper limit.

The initial dose of trastuzumab will be administered over 90 (±10) minutes, and patients will be observed for at least 30 minutes from the end of the infusion for infusion-related symptoms such as fever or chills. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. If the infusion is well tolerated, subsequent infusions may be administered over 30 (±10) minutes, and patients will be observed for a further 30 minutes. All infusion-related symptoms must have resolved before pertuzumab or chemotherapy is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated with analgesics and antihistamines for subsequent infusions.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.10 and Appendix 11. No dose reductions are allowed for trastuzumab. If the patient misses a dose of trastuzumab for any cycle and the time

between doses is ≥6 weeks, a reloading dose of trastuzumab (8 mg/kg) should be given. Subsequent maintenance trastuzumab (6 mg/kg) doses will then be given Q3W, starting 3 weeks later.

If the interval between the first dose of adjuvant trastuzumab and the last dose of neoadjuvant trastuzumab is 6 weeks or more, a reloading dose of 8 mg/kg of trastuzumab is required.

4.3.2.4 Trastuzumab Emtansine (Kadcyla®)

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W. The dose of trastuzumab emtansine administered will be determined on the basis of the baseline weight of the patient. Weight will be measured at each visit and the dose must be re-adjusted for weight changes > 10% compared with the previous visit or baseline. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, in accordance with local practice. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed, following the dose reduction levels provided in Table 6. Once a dose has been reduced for an adverse event(s), it must not be re-escalated.

See Table 2 for guidelines for administration of first and subsequent infusions of trastuzumab emtansine.

Table 2 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Administer the initial dose as a 90-minute IV infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms. • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute infusions. • Patients should be observed during the infusions and for at least 30 minutes after the infusion.

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

Trastuzumab emtansine will be administered after the infusion of atezolizumab/placebo.

4.3.2.5 Chemotherapy

Chemotherapy will be administered in the neoadjuvant setting as follows:

- Doxorubicin 60 mg/m^2 IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4); with
- Cyclophosphamide 600 mg/m^2 IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4); followed by
- Paclitaxel 80 mg/m^2 IV weekly for 12 continuous weeks (Cycles 5–8)

The dose of chemotherapy is calculated according to the patient's BSA. The BSA and the amount of drug administered must be recalculated if the patient's body weight has changed by $>10\%$ (increased or decreased) from baseline. Recalculation of the amount of drug administered on the basis of smaller changes in body weight or BSA is at the investigators' discretion.

There is no mandatory delay between atezolizumab/placebo and ddAC chemotherapy, assuming the infusion is well tolerated.

Doxorubicin

Doxorubicin will be given as an IV bolus over 3–5 minutes or as an infusion over 15–30 minutes, in accordance with local SOC. Dose delays and reduction for toxicity are permitted, and patients should receive G-CSF support according to local practice guidelines.

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

Cyclophosphamide

Cyclophosphamide will be given as an IV bolus over 3–5 minutes or as an IV infusion, in accordance with local SOC. Patients with BSA of >2 m^2 should have their dose capped at 1200 mg.

Dose delays and dose reductions for toxicity are permitted, and patients should receive G-CSF support according to local practice guidelines. Oral cyclophosphamide is not permitted. Refer to the local prescribing information for details regarding the preparation and administration of cyclophosphamide.

Paclitaxel

Paclitaxel will be administered as an IV infusion over 60 ($\pm$10) minutes or according to local SOC, after atezolizumab/placebo, pertuzumab and trastuzumab administration, at

a dose of 80 mg/m^2. See Appendix 11 for guidance on dose reductions. Premedication, including corticosteroids, should be administered according to routine practice.

Patients must be closely observed from the start of the infusion for hypersensitivity reactions, which may occur within minutes. Severe hypotension, bronchospasm, or generalized rash/erythema requires immediate discontinuation of paclitaxel and appropriate treatment. The infusion may be slowed for minor symptoms, such as flushing or local cutaneous reactions. Patients experiencing severe hypersensitivity reactions should be discontinued from study treatment but maintained in the study unless consent is withdrawn. Premedication consisting of a corticosteroid may be given according to institutional guidelines.

Premedications/Supportive Care

In general, chemotherapy supportive care should be administered per ASCO, EORTC, or ESMO guidelines or local SOC. For further details regarding permitted therapies, see Section 4.4.1.

Chemotherapy-induced nausea and vomiting prophylaxis and treatment should be administered as clinically indicated (see Section 4.4.2 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, with the exception of guidance currently in the protocol.

Prophylactic G-CSF or GM-CSF may be used to mitigate the risk of hematologic toxicities according to local policies. Treatment of neutropenia with G-CSF or GM-CSF is permitted according to local policies. In all cases, G-CSF or GM-CSF will not be considered as a study drug and will not be provided by the Sponsor.

4.3.3 Other Required Medication

After surgery, patients with hormone receptor–positive disease should receive adjuvant hormone therapy according to guidelines provided in Section 4.4.1. Postoperative radiotherapy is also indicated according to the guidelines provided in Section 4.4.1.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, pertuzumab, trastuzumab, trastuzumab emtansine, doxorubicin, cyclophosphamide, and paclitaxel) 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.

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.

4.3.5 Continued Access to Atezolizumab, Pertuzumab, Trastuzumab, and Trastuzumab Emtansine

Currently, the Sponsor does not have any plans to provide Roche IMPs (atezolizumab, pertuzumab, trastuzumab, and trastuzumab emtansine) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing pertuzumab, trastuzumab, and trastuzumab emtansine in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the website below. Following the discontinuation of atezolizumab based on the iDMC's recommendation, continued access to atezolizumab will not be considered.

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 30 days prior to initiation of study treatment (for the purposes of screening) until the treatment discontinuation visit. Medication used by the patient within 7 days prior to initiation of study treatment should be recorded. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Record all prior anti-cancer therapies, as applicable.

4.4.1 Permitted Therapy

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

- Acceptable methods of contraception must be used when the female patient or male partner is not surgically sterilized or does not meet the study definition of postmenopausal (≥ 12 months of amenorrhea).
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
  - Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma

- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Medication to treat diarrhea (e.g., loperamide)
- Colony-stimulating factors (e.g., G-CSF)
- Estrogen-receptor antagonists (e.g., tamoxifen), aromatase inhibitors (e.g., anastrazole, exemestane), and gonadotropin-releasing hormone agonists (e.g., buserelin, triptorelin) after surgery, as per local practice and guidelines; luteinizing hormone–releasing hormone agonist as part of an attempt at ovarian function preservation starting prior to chemotherapy
- Radiotherapy after chemotherapy and surgery, during adjuvant therapy

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

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 4.4.2 and Section 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 10).

Radiotherapy

Postoperative patient management may include radiotherapy as clinically indicated, and management of patients who do not achieve a pCR should follow current SOC guidelines. Radiotherapy may be given concurrent with HER2 therapy and atezolizumab/placebo.

Hormone Therapy

Sites should prescribe hormonal therapy per standard local clinical practice. Hormonal therapy is not considered study drug and will not be provided by the Sponsor. Aromatase inhibitors will be allowed as adjuvant hormone therapy for postmenopausal patients who are hormone receptor–positive, in countries where it has been registered for this indication. Its use must be consistent with the registered label. Hormone therapy is given after chemotherapy and surgery, during adjuvant therapy. No other hormone therapy for primary breast cancer is allowed, unless approved for adjuvant therapy.

Female patients must be classified according to one of the following menopausal status definitions:

- Premenopausal:
  - < 12 months since last menstrual period AND no prior bilateral ovariectomy

    AND

    Not receiving estrogen replacement
- Postmenopausal:
  - ≥ 12 months since last menstrual period with no prior hysterectomy

    OR

    Prior bilateral ovariectomy

    OR

    Biochemical evidence of postmenopausal status, according to local policies

Female patients should be treated according to the recommendations in Table 3; however, investigators may follow local practice guidelines. Male patients should be treated according to local policies.

Table 3 Hormonal Therapy

Patient Status [a]	Hormone Therapy
Hormone receptor negative	Not allowed
Hormone receptor–positive and premenopausal	Permitted: • Tamoxifen for 5–10 years with or without ovarian suppression, as per local policy • Aromatase inhibitor for 5 years and ovarian suppression or ablation, followed by tamoxifen to complete 10 years
Hormone receptor–positive and postmenopausal	The following regimens are permitted: • Aromatase inhibitor for 5–10 years • Aromatase inhibitor for 2–3 years, followed by tamoxifen to complete a total of 5 years • Tamoxifen for 2–3 years, followed by an aromatase inhibitor to complete a total of 5 years • Tamoxifen for 5–10 years, as per local policy • Tamoxifen for 5 years, followed by an aromatase inhibitor for 5 years

[a] Hormone receptor positivity is defined as positive estrogen receptor or progesterone receptor or both. The investigator may treat the patient with adjuvant hormone therapy according to local or central results of hormone receptor testing, but central results will be used in data analyses for the study.

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids and TNF-α Inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, with the exception of scenarios described elsewhere in the protocol (see Section 4.3.2.4), in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended at the discretion of the investigator for the treatment of specific adverse events when associated with atezolizumab therapy (see Appendix 12 for details).

4.4.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

The chemotherapeutic agents used in this study are associated with potential drug interactions. The metabolism of paclitaxel is catalyzed by CYP450 isoenzymes CYP2C8 and CYP3A4. The PK of paclitaxel was shown to be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. Doxorubicin is a major substrate of CYP3A4 and CYP2D6 and P-glycoprotein. Cyclophosphamide is a pro-drug that is activated by cytochrome P450s, including CYP2B6, 2C9, and 3A4.

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, such medications should be avoided when chemotherapy is being administered.

Concomitant use of strong CYP3A4/5 inhibitors (such as ketoconazole and itraconazole) with trastuzumab emtansine should be avoided. An alternate medication with no or minimal potential to inhibit CYP3A4/5 should be considered. If a strong CYP3A4/5 inhibitor is co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions. Excessive alcohol intake should be avoided (occasional to moderate use is permitted).

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

4.4.2.3 Herbal Therapies

The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator as long as they are not intended to treat cancer.

4.4.2.4 *Therapies Given for Thrombocytopenia Induced by Chemotherapy*

Concomitant use of therapies for prevention and treatment of thrombocytopenia induced by chemotherapy (e.g., thrombopoietin receptor agonists, recombinant thrombopoietins, recombinant interleukin-11) should be avoided. Adherence to the relevant safety management guidelines to institute appropriate dose modifications of trastuzumab emtansine in case of thrombocytopenia is recommended (Appendix 14). If any of those agents needs to be co-administered with trastuzumab emtansine in line with local standard clinical practice, patients should be closely monitored for adverse reactions and overlapping toxicities.

4.4.3 Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including but not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, 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 the patient has discontinued study treatment, with the exception of previously listed hormone therapy, radiotherapy, and surgery under certain circumstances (see Section 4.4.1 for details).
- Investigational therapy is prohibited during study treatment.
- 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 final dose of atezolizumab/placebo.
- Systemic immunostimulatory agents (including but not limited to interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment with atezolizumab/placebo because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including but not limited to azathioprine, methotrexate, and thalidomide) are prohibited during study treatment with atezolizumab/placebo because these agents could potentially alter the efficacy and safety of atezolizumab.
- Estrogen replacement therapy (hormone replacement therapy)

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1, Appendix 2, and Appendix 3. All activities should be performed and documented for each patient.

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

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Leftover tumor tissue samples, local HER2 test information, baseline demographic, and disease-related characteristics data for all screened patients will be collected by the Sponsor, in order to support a potential registration of a companion diagnostic. The investigator will maintain a *detailed* record of all patients screened and *document* eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), cardiovascular history, menopausal status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines) 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.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. In the physical examination, particular care should be taken with regard to cardiovascular signs and symptoms (e.g., elevated jugular venous pressure, sinus tachycardia, tachypnea, the presence of an S3 heart sound, crackles on chest auscultation, etc.). Bilateral breast examination, including evaluation of locoregional lymphatics, should be conducted (see Section 4.5.5). Any

abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and, if clinically indicated, during or after the infusions. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1). The vital signs measured prior to the infusion of the first study drug at each cycle are required to be reported on the Vital Sign eCRF. Other vital signs are not required to be entered into the eCRF unless abnormal and clinically significant, in which case they are to be reported as adverse events.

4.5.5 Locoregional Tumor Status Assessments

Physical Examination

Assessment of the primary tumor and regional lymph nodes must be done by physical examination during the baseline evaluation, within 3 days prior to each cycle of study treatment during the neoadjuvant phase, and within 14 days prior to surgery. The tumor site must be marked with a radiopaque marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy.

Clinical assessment of tumor measurement in the breast and/or lymph nodes should be conducted in a consistent manner at each evaluation. Clinical measurements of tumor in the breast should be performed, preferentially using calipers or a ruler/tape measure. If possible, these measurements should be conducted by the same assessor at baseline and throughout the neoadjuvant phase.

Tumor measurements at baseline and within 14 days prior to surgery are to be recorded in the eCRF. The main purpose of performing a physical examination prior to each cycle is for patient safety and to provide information that may help to rule out progressive disease that would lead to study treatment discontinuation.

Mammogram

Bilateral mammogram should be obtained within 28 days prior to randomization. To minimize unnecessary radiation exposure and provided that the clinical status of the patient has not changed, the screening mammogram can be performed up to 42 days prior to the start of study treatment. Subsequent mammograms are optional during

neoadjuvant treatment and prior to surgery and should be performed per investigator's discretion. Bilateral mammogram should occur at the study completion/early termination visit and every 12 months (±4 weeks) during the follow-up period. Patients who have undergone mastectomy do not require mammograms on the side of mastectomy.

Other Breast Imaging

Eligibility with regards to the primary breast tumor size (>2 cm) is to be confirmed through imaging (mammogram, positron emission tomography [PET] scan, CT scan, magnetic resonance imaging [MRI], ultrasound, or X-ray). The tumor should be accurately measured in at least one dimension and the longest diameter recorded.

Additional breast imaging throughout the study, such as MRI and ultrasound, are per investigator discretion. MRI examination is not mandated by the protocol and should be per local practice. If MRI is conducted, suggested timelines for MRI are within 28 days prior to protocol therapy, after Cycle 3, and 14 days prior to surgery.

Surgical Treatment Plan

A surgeon with experience in breast cancer surgery should evaluate patients. The proposed surgical treatment plan at baseline should be documented and reported in the eCRF. Patients should be reassessed after completion of neoadjuvant therapy and prior to surgery. The surgeon should evaluate the patient and create a surgical treatment plan. Then after completion of NAST, the surgeon should reassess the patient and modify the surgical treatment plan as needed. These treatments should be documented and reported in the eCRF.

4.5.6 Distant Sites Tumor Assessment

Baseline distant sites tumor staging procedures should be performed in alignment with NCCN or national guidelines, within 28 days prior to randomization.

As a reference, as per NCCN guidelines, staging procedures are based on clinical stage:

- For Stage II and Stage IIIA: Bone scan is to be performed in presence of bone pain and/or elevated ALP; abdominal/pelvic CT scan in case of elevated ALP, abnormal liver function tests, abdominal symptoms or abnormal physical examination; and chest CT scan.
- For Stage IIIB and Stage IIIC: Bone scan and CT scan of chest, abdomen, and pelvis should be conducted for all patients.

In addition, liver function tests, brain imaging, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

4.5.7 Disease Follow-Up and Confirmation of Disease Progression or Recurrence

During neoadjuvant treatment, diagnosis of disease progression or second primary breast cancer should be supported by clinical, laboratory, radiological, and/or histological findings. Post-operatively, all patients must be followed to assess disease recurrence, second primary cancer, and survival. The designation of disease recurrence, whether local, regional or distant, or a diagnosis of a second primary cancer can be made only when clinical, laboratory, radiological, and/or histological findings support the diagnosis.

During the post-operative portion of this study, disease status should be clinically evaluated and documented every 3 months for 2 years and then every 6 months thereafter until the end of the study.

The diagnosis of a breast cancer progression, recurrence, or second primary tumor should be confirmed histologically whenever clinically possible. Differential diagnosis of clinical enlargement of an in-breast tumor during neoadjuvant therapy may include inflammatory response secondary to treatment-related tumor necrosis, infection/mastitis, or true tumor progression. Additional diagnostic workup (e.g., biopsy for histologic confirmation of cancer versus immune-mediated inflammatory process), treatment, and/or multidisciplinary discussion should be considered to help elucidate whether disease progression is occurring and guide whether neoadjuvant treatment should be continued or not.

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 disease progression, recurrent disease, or a diagnosis of a second primary cancer should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence.

Recurrent disease includes local, regional, or distant recurrence and contralateral breast cancer. While ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or recurrent disease, these events should be recorded. Patients who have a diagnosis of in situ breast disease or second (non-breast) malignancies should be maintained on a regular follow-up schedule whenever possible in order to fully capture any subsequent recurrent disease events.

The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events on follow-up are provided in Table 4.

Table 4 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. • 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 across the midline will be considered as evidence of local recurrence. • Confirmed by positive histology or cytology
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. • Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT scan or MRI if no biopsy was performed).	

CT = computed tomography (scan); DCIS = ductal carcinoma in situ; EFS = event-free survival; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; OS = overall survival; PET = positron emission tomography.

Table 4 Definitions of and Procedures for Confirming Disease Recurrence, Death, and Other Noteworthy Events on Follow-Up (cont.)

c) Distant recurrence	• Defined as evidence of tumor in all areas, with the exception of those described in a) and b) above. • Confirmed by the following criteria: Skin, subcutaneous tissue, and lymph nodes (other than local or regional) Positive cytology, aspirate, or biopsy, OR Radiological (CT scan, MRI, PET scan, or ultrasound) evidence of metastatic disease Bone X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR Bone scan (requires additional radiological investigation, alone not acceptable in case of diagnostic doubt), OR Biopsy proof of bone metastases or cytology Bone marrow Positive cytology or histology or MRI Lung Radiologic (CT or PET scan) evidence of multiple pulmonary nodules consistent with pulmonary metastases Positive cytology or histology in case of diagnostic doubt (particularly for solitary lung lesions) if a biopsy is not performed. Serial scans should be obtained if possible to document stability or progression. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy. Liver Radiologic evidence consistent with liver metastases, OR Liver biopsy or fine-needle aspiration 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. Central nervous system Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR Biopsy or cytology in case of inconclusive imaging (e.g., for a diagnosis of meningeal involvement) and, depending from the general status of the patient, additional investigations (including cytology of the cerebrospinal fluid)

CT = computed tomography (scan); DCIS = ductal carcinoma in situ; EFS = event-free survival; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; OS = overall survival; PET = positron emission tomography.

Table 4 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) Death from any cause	• Any death occurring without prior breast cancer recurrence is considered an event for the following endpoints: DFS, EFS, and OS. • Any death occurring during study (with or without prior breast cancer recurrence) is considered an event for the following endpoint: OS.

CT = computed tomography (scan); DCIS = ductal carcinoma in situ; EFS = event-free survival; LCIS = lobular carcinoma in situ; MRI = magnetic resonance imaging; OS = overall survival; PET = positron emission tomography.

4.5.8 Surgical Specimen Pathology

Primary endpoint of the study (pCR) will be as identified by local pathology review using guidelines provided in the pathology manual. A complete pathologic response is defined as the absence of invasive disease in the breast and axilla (tpCR; i.e., ypT0 or ypTis, ypN0) based on microscopic examination of the surgical specimen following neoadjuvant therapy. Guidelines regarding pathology specimen preparation and labeling are outlined in the pathology manual. The Sponsor will prospectively collect local pathology reports. If additional information on lymph nodes at surgery is present in other reports, these should also be submitted to the Sponsor.

4.5.9 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 as clinically indicated:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase (LDH)
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology

- HBV serology: HBsAg, 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, within 7 days prior to initiation of study treatment. Urine pregnancy tests will be performed within 24 hours of Day 1 of every cycle until treatment discontinuation. A pregnancy test must be done at the completion/early termination visit, and at 3 months and 7 months after the discontinuation of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and 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 or a designee for analysis:

- Serum sample 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, trastuzumab, pertuzumab, and trastuzumab emtansine PK analysis through use of validated assays
- Serum samples for assessment of ADAs to atezolizumab, trastuzumab, pertuzumab, and trastuzumab emtansine through use of validated assays
- Blood and plasma samples for exploratory research on biomarkers at baseline and during treatment (see Appendix 3)
- Tumor tissue sample obtained at baseline for determination of HER2 status and PD-L1 expression, ER, and PgR status and for biomarker research (including but not limited to PIK3CA mutation status, TILs, and CD8)
  - A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted. In case of any deviation in submission of tissue material, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.

  - Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Acceptable samples include those collected via core-needle biopsy (at least three cores, embedded in a single paraffin block). Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears) is not acceptable.
- Tumor tissue sample obtained at time of surgery and at time of recurrence (if deemed clinically feasible) for exploratory biomarker research
  - A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted (see further details in Appendix 3).

Leftover tumor tissue samples from all screened patients may be used for future development of diagnostic tests relating to HER2 and PD-L1.

Biomarker analyses may include but will not be limited to analysis of genes or gene signatures associated with HER2 pathway, tumor immune biology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, cytokines associated with T-cell activation, and ctDNA. Analyses may involve extraction of DNA, ctDNA, or RNA, analysis of mutations, and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Research will not be aimed at distinguishing germline mutations from somatic mutations. NGS methods may include whole genome sequencing (WGS)/whole exome sequencing (WES) but only at participating sites (see Section 4.5.13).

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.14), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Tissue samples collected for eligibility testing, at surgery, and at disease recurrence, and blood samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed or earlier depending on local regulations.
- For patients who are not enrolled, remaining tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

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

Data arising from sample analysis, including data on mutations, 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. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.10 Electrocardiograms

A 12-lead ECG is required at screening and when clinically indicated (see Appendix 1). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.11 Echocardiograms or Multiple-Gated Acquisition Scans

LVEF will be assessed by ECHO (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, unless clinically indicated.

Investigators must be aware of local institutional regulations regarding the maximum allowable frequency of repeat MUGA scans. The repeated administration of radioisotopes is limited in some nuclear medicine laboratories, and patients in this study require monitoring on more than four occasions within 1 year.

4.5.12 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 EQ-5D-5L.

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. In scenarios where laboratory assessments (e.g., blood draws) are done in a different clinic than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with patients. 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.

4.5.12.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 6). 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.

4.5.12.2 FACT-G Single Item GP5

The FACT-G instrument Version 4 (see Appendix 5) 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 patients' 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 5-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 1 minute to complete.

4.5.12.3 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 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog 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.

4.5.13 Samples for Whole Genome Sequencing

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

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

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

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

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

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

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

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

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

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

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

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

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

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.14) will not be applicable at that site.

4.5.14.3 Sample Collection

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

- Biomarker blood samples collected at timepoints defined in the schedule of activities
- Leftover blood, serum, plasma, and tumor tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, WES, or other genomic analysis methods. 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 or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

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

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

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

4.5.14.4 Confidentiality

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

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

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

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

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

4.5.14.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.14.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR

samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.14.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment 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 medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Confirmation of disease progression or disease recurrence
- Withdrawal by patient
- Following receipt of the USM DIL dated 3 February 2021, all patients currently receiving study treatment must discontinue treatment with atezolizumab or placebo.

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

Breast cancer surgery and pathological assessment will be performed and reported according to protocol requirements for patients who discontinue study treatment during the neoadjuvant phase (for any reason other than disease progression) and who proceed to surgery without receiving any other non-study anti-cancer therapy prior to surgery. Patients who discontinue neoadjuvant study treatment due to disease progression contribute a non-pCR result and their disease progression must be reported.

Patients who discontinue study treatment early for any reason, enter the follow-up phase of the study (Appendix 1).

4.6.2 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. 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 only (i.e., survival follow-up permitted)

    OR
  - 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.
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status where permitted by local law.

4.6.3 Partial Withdrawal from Study

All of the above provisions regarding withdrawal from the entire study are applicable to partial withdrawal from the study, except that the patient agrees to be contacted for further information on recurrence as per the study secondary endpoint, survival status and anti-cancer therapy. Whenever possible, information on recurrence should be documented through review of medical records as well as patient contact. It should be documented in both the medical records and the eCRF that the patient agreed to be contacted for further information despite the patient's withdrawal of informed consent.

4.6.4 Study Discontinuation

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

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

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

4.6.5 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab, ddAC-PacHP, and trastuzumab emtansine in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1–5.1.8).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab/placebo, ddAC-PacHP, and trastuzumab emtansine 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. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 11, Appendix 12, Appendix 14, and Appendix 15. See Section 5.1.10–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) during study participation should be considered according to local or

institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

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.

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, and myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis *(HLH)*. Refer to Appendix 12 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 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; severe myelosuppression resulting in serious infection, septic shock, need for transfusions, hospitalization, and death; tumor lysis syndrome; radiation sensitization and radiation recall; embryofetal toxicity; infertility; alopecia; hyperuricemia; vomiting; nausea; and other gastrointestinal effects. Hypersensitivity reactions, such as fever, urticaria and anaphylaxis have been occasionally reported.

Refer to the local prescribing information for doxorubicin for more details regarding the full safety profile of doxorubicin, including boxed warnings and contraindications.

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information and Appendix 11 and will be managed as per local practice.

5.1.2.1 Cardiomyopathy

Patients treated with 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 doxorubicin. 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 with the use of ECHO or MUGA scans as described in Section 4.5.11 and the schedule of activities (see Appendix 1). For the algorithm for continuation and discontinuation of study treatment based on LVEF measurements see Figure 3.

5.1.3 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 (with some fatal cases of urotoxicity); myocarditis, myopericarditis (which may be accompanied by pericardial effusion and cardiac tamponade, leading to severe cardiac heart failure), 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; infertility; impairment of wound-healing; hyponatremia; alopecia; nausea; vomiting; stomatitis and diarrhea; anaphylactic reactions including those with fatal outcomes; and cecitis.

Refer to the local prescribing information for cyclophosphamide for more details regarding the full safety profile of cyclophosphamide, including boxed warnings and contraindications.

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information and Appendix 11, and managed as per local practice.

5.1.4 Risks Associated with Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred. Fatal reactions have occurred in patients despite premedication. Therefore, study patients must be premedicated according to local paclitaxel prescribing information and institutional SOC practice. Such premedication may consist of a corticosteroid (dexamethasone 8–10 mg by mouth administered approximately 12 and 6 hours before paclitaxel), diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and a H_2 antagonist (cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before paclitaxel). Patients who experience severe hypersensitivity reactions to paclitaxel despite premedication must not be re-challenged with the drug.

Warnings related to paclitaxel use include myelosuppression (primarily neutropenia), which is dose-dependent and is the DLT during paclitaxel treatment; and increased risk

in patients with hepatic impairment. Infectious episodes may occur and included sepsis, pneumonia, and peritonitis. The use of supportive therapy, including G-CSF or GM-CSF, is recommended for patients who have experienced severe neutropenia.

Other warnings for paclitaxel use include severe cardiac conduction abnormalities, which required pacemaker placement in some cases, peripheral neuropathy, pseudomembranous colitis, mucositis, interstitial pneumonitis. When paclitaxel is used in combination with doxorubicin or trastuzumab, attention should be placed on the monitoring of cardiac function. In addition, paclitaxel can cause fetal harm when administered to a pregnant woman.

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Other significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients, and included syncope, rhythm abnormalities, and venous thrombosis.

Paclitaxel treatment is frequently associated with peripheral neuropathy, and other serious neurologic events following paclitaxel administration have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site; more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have also been reported, with onset during or up to 10 days after paclitaxel infusions.

Caution should be exercised when paclitaxel is concomitantly administered with known substrates, inhibitors, and inducers of CYP3A4 or CYP2C8; see Section 4.4.2.1.

Paclitaxel is contraindicated in patients with severe hepatic impairment.

For more details regarding the safety profile of paclitaxel, refer to the local paclitaxel prescribing information.

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information and Appendix 11 and will be managed as per local practice.

5.1.5 Risks Associated with Pertuzumab, Trastuzumab, and Trastuzumab Emtansine

The known risks associated with trastuzumab treatment include cardiac toxicity (as described below), infusion-related reactions, hypersensitivity and anaphylaxis, febrile neutropenia, diarrhea, pulmonary toxicity, as well as risk of oligohydramnios. Refer to

the Trastuzumab Investigator's Brochure for a full description of the trastuzumab safety profile, warnings, precautions, and guidance for investigators.

For pertuzumab, infusion-related reactions, anaphylaxis and hypersensitivity, diarrhea, interstitial lung disease, left ventricular systolic dysfunction and symptomatic left ventricular systolic dysfunction/congestive heart failure, skin reactions/rash, leukopenia, and mucositis are adverse events of particular clinical relevance. Refer to the Pertuzumab Investigator's Brochure for a full description of the pertuzumab safety profile, warnings, precautions, and guidance for investigators.

Identified risks with trastuzumab emtansine are interstitial lung disease and acute respiratory distress syndrome, hepatotoxicity, nodular regenerative hyperplasia of the liver, left ventricular dysfunction, infusion-related reactions, hypersensitivity reactions, hemorrhage, thrombocytopenia, and peripheral neuropathy. Refer to the Trastuzumab Emtansine Investigator's Brochure for a full description of the trastuzumab emtansine safety profile, warnings, precautions, and guidance for investigators.

The administration of pertuzumab, trastuzumab, and trastuzumab emtansine should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. Patients will be monitored during each infusion for adverse effects (see Section 4.3.2.2 and 4.3.2.3 for details). The management of infusion-associated symptoms is outlined in Appendix 11 and Appendix 14.

5.1.5.1 Cardiotoxicity

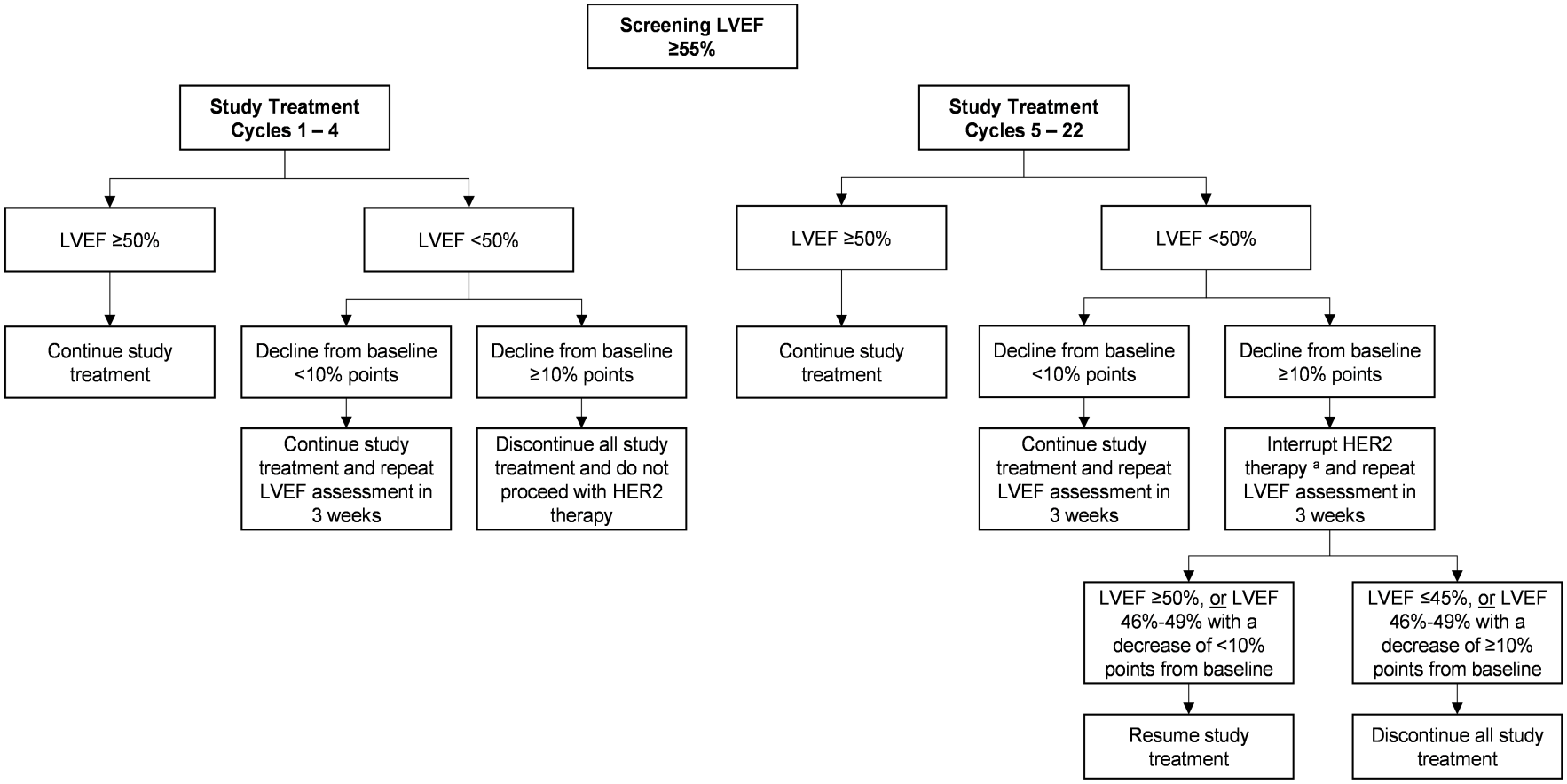
LVEF declines have been reported with drugs that block HER2 activity, including pertuzumab, trastuzumab, and trastuzumab emtansine.

To enter this study, all patients must have a LVEF (by ECHO or MUGA scan) of $\geq$55% and regular monitoring of LVEF is required throughout the study according to the schedule of activities (see Appendix 1). For the algorithm for continuation and discontinuation of study treatment based on LVEF measurements, see Figure 3.

If severe symptomatic heart failure develops (New York Heart Association [NYHA] Class III or IV), the patient must discontinue anti-HER2 therapy. If there is a significant LVEF decrease (LVEF decline $\geq$10 percentage points from baseline to an LVEF value $<$50%), anti-HER2 therapy should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved or has declined further or if clinically significant heart failure develops, the patient must discontinue anti-HER2 therapy. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6–8 weeks). Heart failure or left ventricular dysfunction should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist, and the results of this evaluation should be reported on the eCRF.

Patients who discontinue pertuzumab, trastuzumab, or trastuzumab emtansine for heart failure or LVEF decline should continue to undergo LVEF assessments according to the schedule of activities (see Appendix 1)—irrespective of the initiation of alternative systemic anti-cancer therapy—until resolution, improvement to baseline status, no further improvement can be expected, or death. Additional LVEF assessments may be required for these patients (beyond those specified in the schedule of activities), according to the investigator's clinical judgment. The results of these assessments should be reported.

Figure 3 Algorithm for Continuation and Discontinuation of Study Treatment on the Basis of LVEF Assessment



HER2 = human epidermal growth factor 2; LVEF = left ventricular ejection fraction.

[a] Three intermittent holds of study treatment will lead to discontinuation.

5.1.5.2 EGFR-Related Toxicities

Although pertuzumab targets the HER2 receptor, it inhibits heterodimerization with other members of the HER family (e.g., epidermal growth factor receptor [EGFR; HER1]). Accordingly, it may cause toxicities associated with the use of EGFR inhibitors such as diarrhea, rash, and other dermatologic toxicities (e.g., dry skin, pruritus, nail disorders, or mucositis).

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered, and patients should be treated with fluids and electrolyte replacement, as clinically indicated.

Treatment recommendations for EGFR-associated rash include topical or oral antibiotics and topical steroids or systemic steroids (for severe reactions).

These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated, although they have not been studied in this context.

Mucositis is generally not considered preventable; although for some cytotoxic agents, mucositis may be reduced by cooling the mouth using ice chips before and during the infusion.

5.1.6 Risks Associated with Trastuzumab Emtansine

5.1.6.1 Pulmonary Toxicity

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

Permanently discontinue treatment with trastuzumab emtansine in patients diagnosed with ILD or pneumonitis, except for radiation pneumonitis in the adjuvant setting, where trastuzumab emtansine should be permanently discontinued for Grade ≥ 3, or for Grade 2 not responding to standard treatment. In comparison with drug-induced pneumonitis, radiation pneumonitis is often focal and limited to the area exposed to radiation.

Patients with dyspnea at rest due to complications of advanced malignancy, co-morbidities, and receiving concurrent pulmonary radiation therapy may be at increased risk of pulmonary toxicity.

Guidelines for management of trastuzumab emtansine in patients who develop ILD or pneumonitis are provided in Appendix 14.

5.1.6.2 Hepatotoxicity

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

- Serious hepatobiliary disorders
  - Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and hepatobiliary disorders with a fatal outcome due to drug-induced liver injury, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases may have been confounded by concomitant medications with known hepatotoxic potential.
- Increased serum transaminases
  - Asymptomatic increases in serum transaminase concentration (transaminitis) have been observed. Grade 1 and 2 events have been observed frequently; Grade 3 and 4 events have been observed less commonly. The incidence of increased AST was substantially higher than that for increased ALT. Increases in AST and ALT were commonly observed by Day 8 of each cycle and generally improved or returned to baseline by Day 21. A cumulative effect of trastuzumab emtansine, that is, an increase in the proportion of patients with Grade 1 or 2 elevations in transaminases with successive cycles has been observed; however, there was no increase in the proportion of patients with Grade 3 abnormalities over time.
- NRH
  - Cases of NRH have been identified from liver biopsies in patients treated with trastuzumab emtansine who presented with signs and symptoms of portal hypertension. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules. NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can only be confirmed by histopathology. Biopsy-confirmed NRH leading to fatal hepatic failure has been reported.
  - NRH should be considered in all patients with clinical symptoms of portal hypertension, even with normal transaminases, and no other manifestations of cirrhosis; in patients with a cirrhosis-like pattern seen on a CT scan of the liver; and/or in patients with liver failure following long-term treatment with trastuzumab emtansine.

Guidelines for management of trastuzumab emtansine in patients who develop increased serum transaminases, increased serum bilirubin, or NRH are provided in Appendix 14.

5.1.6.3 Left Ventricular Dysfunction

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

Guidelines for patient monitoring and management of trastuzumab emtansine in patients who develop left ventricular dysfunction are provided in Section 5.1.5.1 and Appendix 14.

5.1.6.4 Infusion-Related Reactions and Hypersensitivity Reactions

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

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

Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine. Patients with a history of intolerance to trastuzumab are excluded from this study (see Section 4.1.2).

Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients should be closely monitored for IRRs during and after each infusion of trastuzumab emtansine.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in Appendix 14.

5.1.6.5 Hematologic Toxicity

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

Patients with thrombocytopenia ($\leq$100,000/mm^3) and patients on anticoagulant treatment should be monitored closely during treatment with trastuzumab emtansine. It is required that platelet counts are monitored prior to each trastuzumab emtansine dose. *Rare cases of severe prolonged thrombocytopenia defined as persisting ($\geq$Grade 3 thrombocytopenia events lasting for more than 90 days) have been reported with*

trastuzumab emtansine on the basis of cumulative data review. In most of these cases, patients received concomitant recombinant human thrombopoietin. Trastuzumab emtansine has not been studied in patients with platelet counts $\leq 100{,}000/mm^3$ prior to initiation of treatment. In the event of decreased platelet count to Grade ≥ 3 ($< 50{,}000/mm^3$), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq 75{,}000/mm^3$).

Declines in other hematopoietic lineages (e.g., leukopenia, neutropenia, and anemia) were less frequent than that observed for platelets.

Guidelines for management of trastuzumab emtansine in patients who develop hematologic toxicity are provided in Appendix 14.

5.1.6.6 Hemorrhage

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

5.1.6.7 Neurotoxicity

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

Patients with Grade ≥ 3 peripheral neuropathy should not be considered for treatment with trastuzumab emtansine.

Guidelines for management of trastuzumab emtansine in patients who develop peripheral neuropathy are provided in Appendix 14.

5.1.6.8 Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and consisted of erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of the infusion.

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. Patients should be managed symptomatically per local institutional guidelines.

5.1.7 Risks Associated with Combination Use of Pertuzumab with Trastuzumab and Paclitaxel

Pertuzumab was well tolerated in combination with trastuzumab (Study WO20697), with an increase in the incidence but not severity of the common adverse events seen with single-agent pertuzumab (notably, diarrhea, rash, and fatigue).

Study WO29217 (BERENICE) is an open-label, nonrandomized, multicenter, multinational Phase II study to evaluate pertuzumab in combination with trastuzumab and standard neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive, locally advanced, inflammatory, or EBC. Eligible patients were allocated, by the investigator, to receive one of the two treatment regimens: ddAC given Q2W for 4 cycles, followed by weekly paclitaxel for 12 weeks, with pertuzumab and trastuzumab given Q3W from the start of paclitaxel; or FEC given Q3W for 4 cycles, followed by docetaxel given Q3W for 4 cycles, with pertuzumab and trastuzumab given Q3W from the start of docetaxel (FEC→docetaxel + pertuzumab and trastuzumab).

- There were no unexpected safety signals in Study WO29217.
- During the overall treatment period, the most frequently reported adverse events (≥ 10% of patients) considered to be related to pertuzumab or trastuzumab included diarrhea, IRR, fatigue, ejection fraction decreased, epistaxis, arthralgia, myalgia, asthenia, anemia, and mucosal inflammation. Grade ≥ 3 adverse events during overall treatment were reported by approximately half of the patients, and the most commonly reported terms were febrile neutropenia, neutropenia, diarrhea, and stomatitis. The serious adverse events during the overall treatment period reported by ≥ 2% of patients in either cohort included febrile neutropenia, diarrhea, neutropenic sepsis, device-related infection, ejection fraction decreased, and pyrexia. The adverse event profile observed in Study WO29217 is consistent with the established safety profile of pertuzumab and trastuzumab in combination with chemotherapy.
- The most common laboratory post-baseline abnormalities for the overall study period were hematological. The highest incidence of Grade 3 or 4 abnormalities was reported for lymphocytopenia, absolute neutrophil count, and low white blood cell count.
- For those patients who received ddAC followed by paclitaxel with pertuzumab and trastuzumab: The cardiac safety observed during the overall study period in patients with normal cardiac function at baseline remained in line with that observed in previous clinical studies with dual HER2-containing treatment regimens and the known clinical profile of pertuzumab and trastuzumab. The incidence of NYHA Class III or IV heart failure occurring during the overall study period was low. Based on the known cardiac safety profile of pertuzumab and trastuzumab from studies with dual HER2-containing treatment regimens, there were no unexpected findings.

5.1.8 Risks Associated with Combination Use of Atezolizumab and Doxorubicin, Cyclophosphamide, Paclitaxel, Trastuzumab, Pertuzumab, or Trastuzumab Emtansine

The following adverse events are important potential overlapping toxicities associated with combination use of atezolizumab and doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, or pertuzumab: cardiotoxic and gastrointestinal (diarrhea, colitis) events. Additional potential overlapping toxicities include respiratory disorders, skin rash, hypersensitivity and IRRs. Myelosuppression (neutropenia, anemia, or thrombocytopenia) is an important potential overlapping toxicity of chemotherapy (doxorubicin, cyclophosphamide, paclitaxel) and HER2 targeted therapy (trastuzumab, pertuzumab). The risk of overlapping toxicities is thought to be manageable based on the mechanism of action of each product.

When there is a possibility of overlapping toxicities, the attribution of an adverse event to particular drug(s) will be based on the investigator's clinical judgment. See Table 5 below for sources in the protocol that provide guidance for managing overlapping toxicities.

Table 5 Guidance for Managing Overlapping Toxicities

Event	Source in Protocol for Guidance
Cardiotoxicity	
Doxorubicin	• Section 5.1.2.1 and Appendix 11 (Doxorubicin and Cyclophosphamide, Cardiotoxicity)
Cyclophosphamide	• Appendix 11 (Doxorubicin and Cyclophosphamide, Cardiotoxicity)
Pertuzumab	• Section 5.1.5.1 and Appendix 11 (Pertuzumab and Trastuzumab, Cardiotoxicity)
Trastuzumab	• Section 5.1.5.1 and Appendix 11 (Pertuzumab and Trastuzumab, Cardiotoxicity)
Atezolizumab	• Appendix 12 (Immune-Mediated Myocarditis, including Table 6)
Paclitaxel	• Section 5.1.4 and local prescribing information for paclitaxel
Diarrhea or colitis	
Pertuzumab	• Section 5.1.5.2 and Appendix 11 (Pertuzumab and Trastuzumab, EGFR-Related Toxicities)
Paclitaxel	• Appendix 11 and local prescribing information for paclitaxel
Atezolizumab	• Appendix 12 (Gastrointestinal Events, including Table 3)

Table 5 Guidance for Managing Overlapping Toxicities (cont.)

Event	Source in Protocol for Guidance
Respiratory disorders	
Atezolizumab	• Appendix 12 (Pulmonary Events, including Table 1), Appendix 15, and the Atezolizumab Investigator's Brochure
Pertuzumab	• Pertuzumab Investigator's Brochure
Trastuzumab	• Trastuzumab Investigator's Brochure
Cyclophosphamide	• Local prescribing information for cyclophosphamide
Paclitaxel	• Appendix 11 (Pulmonary Events/Pneumonitis) and local prescribing information for paclitaxel
Trastuzumab emtansine	• Appendix 15 and the Trastuzumab Emtansine Investigator's Brochure
Skin rash	
Pertuzumab	• Section 5.1.5.2 and Appendix 11 (Pertuzumab and Trastuzumab, EGFR-Related Toxicities)
Atezolizumab	• Appendix 12 (Dermatologic Events, including Table 9)
Paclitaxel	• Local prescribing information for paclitaxel
Hypersensitivity and infusion-related reactions	
Atezolizumab	• Section 4.3.2.1 and Appendix 12 (Infusion-Related Reactions, including Table 7)
Pertuzumab	• Section 4.3.2.2 and Appendix 11 (Pertuzumab and Trastuzumab, Infusion-Associated Symptoms)
Trastuzumab	• Section 4.3.2.3 and Appendix 11 (Pertuzumab and Trastuzumab, Infusion-Associated Symptoms)
Paclitaxel	• Sections 4.3.2.4 (Paclitaxel) and 5.1.4, and the local prescribing information for paclitaxel
Myelosuppression	
Paclitaxel	• Section 5.1.4, Appendix 11, and the local prescribing information for paclitaxel
Doxorubicin	• Local prescribing information for doxorubicin
Cyclophosphamide	• Local prescribing information for cyclophosphamide
Pertuzumab	• Pertuzumab Investigator's Brochure
Trastuzumab	• Trastuzumab Investigator's Brochure

Table 5 Guidance for Managing Overlapping Toxicities (cont.)

Event	Source in Protocol for Guidance
Hepatotoxicity	
Atezolizumab	• Appendix 15 and the Atezolizumab Investigator's Brochure
Trastuzumab emtansine	• Appendix 15 and the Trastuzumab Emtansine Investigator's Brochure

For additional information, dose reductions and management, see Section 5.1.1– 5.1.6 in conjunction with Appendix 11, Appendix 12, Appendix 14, and Appendix 15 as well as the local prescribing information for doxorubicin, cyclophosphamide, and paclitaxel, and the Trastuzumab, Pertuzumab, Atezolizumab, and Trastuzumab Emtansine Investigator's Brochures.

5.1.9 General Plan to Manage Safety Concerns

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v5.0. Patients will be assessed for safety (including laboratory test values) according to the schedule of activities in Appendix 1 and Appendix 2. Laboratory test values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts (see Section 4.5 and Appendix 1 and Appendix 2 for the list and timing of study assessments).

Cardiac monitoring (ECHO or MUGA scan) will be performed on all patients enrolled in the study and will be obtained at baseline and at regular intervals throughout the study. See Appendix 1 for further details.

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Section 5.2.2 and 5.2.3) will be reported in an expedited fashion (see Section 5.4.2).

5.1.10 Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

The severity of adverse events will be graded according to the NCI CTCAE v5.0.

- For any concomitant conditions reported at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator determines that it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be attributable solely to one component of the study treatment and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.

See Appendix 11 and Appendix 12 for dose modification guidelines.

5.1.10.1 Dose Modifications of Trastuzumab Emtansine and Atezolizumab/Placebo

Treatment management guidelines reflect the guidance prior to the issuance of the USM DIL dated 3 February 2021. Following the mandated discontinuation of blinded study treatment with atezolizumab or placebo, these guidelines still apply; however, these guidelines apply without treatment with atezolizumab/placebo.

If trastuzumab emtansine is held for toxicity, then atezolizumab/placebo must also be held. If trastuzumab emtansine is discontinued for toxicity, atezolizumab/placebo must not be continued as single agent and must either be discontinued also or may be continued in combination with trastuzumab and pertuzumab to complete a total of 1 year of HER2-targeted therapy if the investigator considers the toxicity to be related to trastuzumab emtansine without compromising the continued use of trastuzumab.
If treatment with atezolizumab/placebo had been discontinued prior to the discontinuation of trastuzumab emtansine or if both treatments are discontinued concurrently, it is at the investigator's discretion to switch treatment to trastuzumab and pertuzumab if the toxicity is not considered related to the trastuzumab component of trastuzumab emtansine.

If study treatment is temporarily interrupted because of toxicity caused by trastuzumab emtansine or atezolizumab/placebo, the treatment cycles will be restarted such that the atezolizumab/placebo and trastuzumab emtansine infusions remain synchronized.
If significant trastuzumab emtansine–related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days after the last dose was received. "Significant" and "related" will be based on the judgment of the investigator (in consultation with the Sponsor's Medical Monitor or designee when appropriate). For example, alopecia even if considered related to trastuzumab emtansine would most likely not be considered to be significant. In general, when the significant related toxicity (or any other toxicity that the investigator chooses to delay

dosing for) resolves to Grade 1 or baseline, the patient may resume trastuzumab emtansine if the delay is not >42 days from the last dose received. Patients should be re-evaluated weekly during the delay, whenever possible. If dosing resumes, the patient may receive trastuzumab emtansine either at the same dose level as before or at one lower dose level (see Table 6), at the discretion of the investigator. Subsequent cycles should remain Q3W. If a patient requires a dose reduction, dosing will be reduced by one dose level as per Table 6. A maximum of two dose reductions is allowed for trastuzumab emtansine. No dose re-escalation is permitted. A patient treated with 2.4 mg/kg of trastuzumab emtansine who develops an adverse event requiring a dose reduction must discontinue trastuzumab emtansine. For patients who experience Grade 3 or 4 hematologic events, other than thrombocytopenia, treatment should be interrupted and the patient should be checked at least weekly for recovery. If values do not recover to baseline or Grade ≤1 within 42 days from the last dose received, the patient will be discontinued from trastuzumab emtansine. For thrombocytopenia, see Appendix 14. No dose modification is allowed for atezolizumab.

If dosing with trastuzumab emtansine has been delayed for more than 42 days from the last dose, and the investigator wishes to re-start treatment with trastuzumab emtansine based on a positive benefit–risk assessment for the individual patient, the Medical Monitor is *available for consultation*.

Table 6 Dose Modification Scheme for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level (mg/kg, Q3W)
Starting dose	3.6
First dose reduction	3.0
Second dose reduction	2.4
Requirement for further dose reduction	Discontinue treatment

Q3W = every 3 weeks.

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

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 Good Clinical Practice, 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 Section 5.3.5.9 and Section 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)
- 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)
- Myositis

- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders
- Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of trastuzumab, pertuzumab, or trastuzumab emtansine
- 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 following selected adverse events.

5.2.4.1 Cardiac, General

Symptomatic left ventricular systolic dysfunction (referred to as heart failure) 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 (i.e., report heart failure rather than dyspnea on exertion, bilateral ankle edema, and tachycardia; see Section 5.3.5.2). A cardiac consultation is recommended for patients who develop symptomatic left ventricular systolic dysfunction (heart failure). 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 at any point during the study (including the follow-up period), even beyond the 90 days after the final dose of study treatment (see Section 5.6) must be reported, irrespective of causal relationship, and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

5.2.4.2 Asymptomatic Left Ventricular Systolic Dysfunction

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 ≥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 event was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of trastuzumab, pertuzumab, or trastuzumab emtansine must be reported as an adverse event of special interest (see Section 5.2.3); a comment in the adverse event comments field should confirm that this event was asymptomatic.

Table 7 summarizes the reporting conventions for left ventricular systolic dysfunction and heart failure.

Table 7 Reporting Conventions for Left Ventricular Systolic Dysfunction/Congestive Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF of < 10 percentage points from baseline or to an LVEF of ≥ 50%	No additional reporting required; LVEF results to be reported on eCRF.	NA	NA
Asymptomatic decline in LVEF of ≥ 10 percentage points from baseline to an LVEF of < 50%	AE [a] (eCRF AE eForm)	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of trastuzumab, pertuzumab, or trastuzumab emtansine	AE (eCRF AE eForm) and reported as a non-serious AESI on an SAE form	Ejection fraction decreased [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure/CHF (symptomatic LVSD) [b]	AE (eCRF AE eForm) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA class

AE = adverse event; AESI = adverse event of special interest; CHF = congestive heart failure; eCRF = electronic case report form; e-Form = electronic form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NA = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.

[a] Report the status as asymptomatic and provide the LVEF value in the comments field as appropriate.

[b] Any symptomatic LVSD event must be reported as "heart failure."

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 final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

For reporting of heart failure, see Section 5.2.4.1 and 5.6.

Study drug–related serious adverse events will be reported indefinitely (even if the study has been closed). 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 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- 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 9 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 will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording 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 cytokine release syndrome. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome") on the Adverse Event eCRF. If possible, 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.

If a patient experiences both a local and systemic reaction to the same dose 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.

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 12.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by 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., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the 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 ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as 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 progression of HER2-positive breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee 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. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.10 Lack of Efficacy or Worsening of HER2-Positive Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. Instances of disease recurrence will be verified by pathologic confirmation in accordance to the pathology manual. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., 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 when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying 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 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.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

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)
- Accidental overdoses or medication errors (see Section 5.4.4 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/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients *access to* Medical *Monitors is* available 24 hours per day, 7 days per week. *Details will be provided separately.*

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 paper Clinical Trial Adverse Event/Special *Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the

EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab/placebo, 6 months after the final dose of doxorubicin, 12 months after the final dose of cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine (whichever is longer). A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 3, 6, and 12 months after birth.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of doxorubicin and/or cyclophosphamide, 6 months after the final dose of paclitaxel, and 7 months after the final dose of trastuzumab, pertuzumab, or trastuzumab emtansine (whichever is longer). A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study 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 when updated information on the course and outcome of the pregnancy 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 3, 6, and 12 months after birth.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as 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).

5.4.4 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. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab/placebo, trastuzumab, pertuzumab, and trastuzumab emtansine, 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/placebo, trastuzumab, pertuzumab, and trastuzumab emtansine, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF. *In the instance where this results in a serious adverse event, the event must be* reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded 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 the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

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. 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 period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, 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 serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), deaths either attributed by the investigator solely to progression of HER2-positive breast cancer or due to an adverse event considered by the investigator unrelated to prior exposure to study treatment, should be reported through use of the Long-Term Survival Follow-Up eCRF.

Heart failure occurring at any point during the study, even beyond the 90 days after the final dose of study treatment, must be reported, irrespective of causal relationship, and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death. Heart failure, irrespective of causal

relationship, that that occurs after study closure should be reported to Roche as a spontaneous report to be included in the Roche Global Safety Database.

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 (e.g., completion of the study), the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all 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, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Pertuzumab Investigator's Brochure
- Trastuzumab Investigator's Brochure
- Trastuzumab Emtansine Investigator’s Brochure
- European Summary of Product Characteristics (EU-SmPC) for doxorubicin, cyclophosphamide, and paclitaxel

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 ANALYSIS POPULATIONS

The analysis populations are defined as follows:

- The ITT population is defined as all randomized patients, whether or not the assigned study treatment was received.
- The PD-L1–positive population is defined as patients in the ITT population whose PD-L1 status is IC 1/2/3 at the time of randomization.

- The PRO-evaluable population is defined as patients in the ITT population with a baseline and ≥1 postbaseline PRO assessment.
- The safety-evaluable population is defined as patients who received any amount of any study drug.

For all efficacy analyses, patients will be assigned to the treatment group to which they were randomized.

For safety analyses, 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 arm.

6.2 DETERMINATION OF SAMPLE SIZE

The global study will randomize approximately 453 patients in total. Assuming a prevalence of 40% of PD-L1–positive patients (defined as tumors with a PD-L1 expression level of IC 1/2/3), the PD-L1–positive population is estimated to comprise approximately 181 patients.

6.2.1 Type I Error Control

The Type I error (α) for this study is 0.05 (two-sided). The Type I error will be controlled for the following efficacy endpoints:

- Co-primary efficacy endpoint of pCR, as defined in Section 2.1.1, in the PD-L1–positive population with an allocated α of 0.048
- Co-primary efficacy endpoint of pCR, as defined in Section 2.1.1, in the ITT population with an allocated α of 0.002

In the PD-L1–positive population, this sample size will allow for 80% power to detect an improvement in pCR proportion from 70% in the placebo + ddAC-PacHP to 90% (+20%) in the atezolizumab + ddAC-PacHP group at the 4.8% level of significance (two-sided) assuming a dropout of 7% of the patients (i.e., patients without pCR assessment will be regarded as not achieving pCR resulting in an improvement in pCR proportion from 65% to 83%; +18%).

In the ITT population, this sample size will allow for 82.8% power to detect an improvement in pCR proportion from 60% in the placebo + ddAC-PacHP to 80% (+20%) in the atezolizumab + ddAC-PacHP group at the 0.2% level of significance (two-sided), assuming a dropout of 10% of the patients (i.e., patients without pCR assessment will be regarded as not achieving pCR resulting in an improvement in pCR proportion from 54% to 72%; +18%).

6.3 SUMMARIES OF CONDUCT OF STUDY

For all randomized patients (i.e., ITT population), a participant flowchart for depicting the progress of participants through the phases of the trial will be provided by treatment arm,

including a complete description of patient disposition specifying the number of randomized, completed, and discontinued patients from trial treatment and study with reasons for premature discontinuation. Documented major protocol deviations including major deviations with regard to the inclusion and exclusion criteria, conduct of the study, patient management, or patient assessment will be also tabulated by treatment arm.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (in particular, stratification variables) will be summarized by treatment arm for the ITT population. Only descriptive analyses are planned; no formal statistical tests will be applied. Continuous variables will be reported and summarized by use of standard measures of central tendency and dispersion (mean, standard deviation, median, and range including minimum and maximum), and categorical (i.e., discrete) data will be reported and summarized by frequencies and percentages. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.5 EFFICACY ANALYSES

Details of the analyses, including methods for handling missing data, are specified in the SAP.

6.5.1 Co-Primary Efficacy Endpoint

The co-primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with placebo when given in combination with neoadjuvant ddAC-PacHP in patients eligible for surgery with early HER2-positive breast cancer at high risk of recurrence (T2–4, N1–3) as measured by pCR in the ITT and in the PD-L1–positive populations. pCR is established following completion of neoadjuvant therapy and surgery.

pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of NAST (i.e., ypT0/is ypN0 in the current AJCC staging system).

Patients with missing pCR assessment will be counted as not achieving a pCR. Treatment comparison of pCR will be made using Cochran-Mantel-Haenszel test stratified by disease stage (T2 vs. T3 or 4), hormone receptor status (positive vs. negative) and PD-L1 status (IC 0 vs. IC 1/2/3), if applicable. The 2-sided significance level in the PD-L1–positive population is 4.8% and in the ITT population 0.2%. The stratification factors will be based on data collected by the IxRS at the time of randomization. Confidence intervals for the difference in pCR rate between the two arms will be determined using the normal approximation to the binomial distribution.

A summary table that presents the number and proportion of pCR in each treatment arm, together with the 2-sided 95% CI with use of the Clopper-Pearson method will be produced (Clopper and Pearson 1934).

6.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- pCR (ypT0/is ypN0) based upon hormone receptor status (ER/PgR positive or ER/PgR negative) in all patients (ITT population) and based upon PD-L1 status (IC 0; IC 1/2/3)
- pCR (ypT0/is ypN0) in the PD-L1–negative (IC 0) population
- EFS, defined as the time from randomization until documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause in all patients (ITT population) and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- DFS, defined as the time from surgery until documented disease recurrence or death from any cause in all patients (ITT population) who undergo surgery and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- OS, defined as the time from randomization to the date of death from any cause in all patients (ITT population) and based upon hormone receptor status (ER/PgR positive or ER/PgR negative) and PD-L1 status (IC 0; IC 1/2/3)
- PROs of function (role, physical) and HRQoL in PRO-evaluable population

6.5.2.1 pCR in the Subgroups

pCR is defined in analogous manner to the primary endpoint and will be analyzed with the same methodology in the subgroups. The stratification factors in the subgroup analysis will be as defined below:

- pCR by hormone receptor status: The stratification factors will be disease stage and PD-L1 status.
- pCR by PD-L1 status: The stratification factors will be disease stage and hormone receptor status.

6.5.2.2 Event-Free Survival

EFS is defined as the time from randomization to the first documented disease recurrence, unequivocal tumor progression determined by the treating investigator, or death from any cause, whichever occurs first.

Patients without an event at the time of the 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 at the date of randomization.

EFS will be compared between treatment arms with the use of the log-rank test stratified by the randomization stratification factors collected by the IxRS at the time of randomization and by the adjuvant treatment regimen. The HR for EFS will be estimated using a Cox proportional hazards model. The 95% CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate the median EFS (if reached) for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median EFS for each treatment arm (Brookmeyer and Crowley 1982). The Kaplan-Meier approach will be also used to estimate landmark EFS rates, including 3-year EFS rates, and corresponding 95% CIs for each treatment arm. Results from an unstratified analysis will also be provided.

The EFS analysis will be performed approximately 36 months after the randomization of the last patient during the global enrollment phase.

Exploratory subgroup analyses of EFS in pre-defined subgroups of interest will be performed, including adjuvant treatment regimen. Full details will be provided in the SAP.

6.5.2.3 Disease-Free Survival

DFS is defined as the time from surgery (i.e., the first date of no disease) to the first documented disease recurrence or death from any cause, whichever occurs first. Patients who do not undergo surgery at the end of neoadjuvant treatment will be excluded from the analysis of DFS.

Patients without a DFS event at the time of analysis will be censored at the date when they were last known to be alive and event free. Patients who do not have information after surgery will be censored at the date of surgery.

DFS will be analyzed with the use of the same methodology as specified for EFS. The DFS analysis will be performed approximately 36 months after the randomization of the last patient during the global enrollment phase.

Exploratory subgroup analyses of DFS in pre-defined subgroups of interest will be performed, including adjuvant treatment regimen. Full details will be provided in the SAP.

6.5.2.4 Overall Survival

OS is defined as the time from randomization to death from any cause. Patients who are not reported as having died at the time of analyses 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. OS will be analyzed with the use of the same methodology as specified for EFS. The OS analysis will be performed

approximately 36 months after the randomization of the last patient during the global enrollment phase.

Exploratory subgroup analyses of OS in pre-defined subgroups of interest will be performed, including adjuvant treatment regimen. Full details will be provided in the SAP.

6.5.2.5 Patient-Reported Outcomes of Role and Physical Function and GHS/HRQoL: EORTC Data

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 (with 95% CI) 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). PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm. Details of the analysis, including methods for handling missing data, will be specified in the SAP.

6.5.3 Exploratory Efficacy Endpoints

6.5.3.1 Patient-Reported Outcomes of Disease/Treatment–Related Symptoms, and Emotional and Social Function: EORTC Data

Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline (with 95% CI) will be calculated for all disease/treatment–related symptom items and scales, and the emotional and social function scales of the EORTC QLQ-C30 (see Appendix 4) at each assessment timepoint for each arm.

6.5.3.2 Patient-Reported Outcome of Treatment Bother: 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 5). Item GP5 from Version 4 of the FACT-G Questionnaire will be scored according to the Functional Assessment of Chronic Illness Therapy scoring manual (Cella 1997).

6.5.3.3 Health Economic EQ-5D-5L Data

Health utility data from the EQ-5D-5L (see Appendix 6) will be evaluated in pharmacoeconomic models. The results from the health economic data analyses will be reported separately from the clinical study report.

6.6 SAFETY ANALYSES

Safety analyses will be performed on the safety population defined as all patients who received any dose of study medication.

Safety will be assessed through summaries of study treatment exposures, adverse events, changes in targeted laboratory and diagnostic test results, changes in vital signs, and immunogenicity as measured by ADAs and will be presented by treatment arm. Selected safety data will also be presented separately according to adjuvant treatment regimen.

6.6.1 Exposure of Study Medication

Study drug exposure, including but not limited to treatment duration, number of cycles, and dose intensity, will be summarized with descriptive statistics for each study treatment on each treatment arm if deemed appropriate.

6.6.2 Adverse Events

Verbatim descriptions of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v5.0.

Treatment-emergent adverse events, defined as events occurring on or after the first dose of study treatment, will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v5.0 grade, regardless of relationship to study drug as assessed by the investigator. 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 ≥ 3 adverse events, Grade 5 adverse events, serious adverse events
- Adverse events of special interest
- Selected adverse events on the basis of the safety profile of the study drug

All deaths and causes of death will be summarized.

6.6.3 Laboratory Data

Laboratory data with values outside of the normal ranges will be identified. Relevant laboratory values will be summarized by treatment arm over time, with NCI CTCAE v5.0 Grade 3 and Grade 4 values identified, where appropriate. Changes from baseline in

NCI CTCAE v5.0 grade (i.e., shift tables) will be also provided by treatment arm. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables.

A Hy's Law analysis will be provided: 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).

6.6.4 Vital Signs

Changes in selected vital signs will be summarized by change from baseline by treatment arm.

6.7 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, standard deviations, coefficient of variation (%CV), and others as appropriate.

The pertuzumab, trastuzumab, and trastuzumab emtansine concentrations in serum will also be tabulated and summarized. Additional PK and PD analyses may be conducted as appropriate.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include all patients with at least one ADA result, 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 (post-baseline incidence) will be summarized by treatment group. When determining post-baseline 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 post-baseline 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 are missing data at baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline 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.

6.9 BIOMARKER ANALYSES

Biomarker analyses will be performed as follows:

- Analysis of pCR by stromal TIL infiltration levels will be stratified by disease stage, hormone receptor status, and PD-L1 status. Cutoffs for stromal TIL infiltration levels will be specified in the SAP.
- Analysis of pCR by immune gene expression levels will be stratified by disease stage, hormone receptor status and PD-L1 status. Cutoffs for immune gene expression levels will be specified in the SAP.
- Analysis of pCR, EFS, DFS, and OS by PIK3CA mutation status will be stratified by disease stage, hormone receptor status, and PD-L1 status.

Descriptive statistics will be utilized for the analysis and reporting of other exploratory biomarker objectives outlined in Section 2.5. This may include appropriate multivariate analyses. Further details will be specified in the SAP.

6.10 INTERIM ANALYSES

6.10.1 Planned Interim Analyses

In order to extract information from data accumulated thus far for reasons external to the study (administrative objective, to inform the initiation of a possible subsequent trial), an administrative interim efficacy analysis of pCR is planned to take place once 227 patients have been enrolled, completed neoadjuvant treatment, and undergone surgery. The administrative interim analysis is performed without any intention to stop the trial. However, a minimum alpha of 0.0001 will be spent to protect the overall type I error. The interim analysis will be performed by the iDCC, an external statistical group, to ensure the Sponsor study team personnel remain blinded. The results will be reviewed by the iDMC. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter.

The rationale and methods, including those to be used for the assessment and protection of the overall type I error, will be documented in the SAP. Details will also be included in the iDMC Charter.

6.10.2 Optional Interim Analyses

The Sponsor may choose to conduct interim efficacy analyses after the primary analysis for pCR and before the final analysis for EFS and OS, if needed (e.g., for regulatory or publication purposes). The decision to conduct an optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel who will have full access to unblinded data. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, 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 direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, 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. 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.

Roche 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 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or 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 Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.3).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Up to 120 sites globally will participate to randomize approximately 453 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.9. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the EMA, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and/*or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities

	Screening/ Baseline [a]		Treatment Cycles										Treatment Discontinuation/Early Termination Visit [d]	Follow-Up [e]
			Neoadjuvant Phase Cycles1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles								Pre-Surgery Visit/ Surgery [b]	Adjuvant Phase [c] (Cycles 9–22) 21-Day Cycles		
			Day 1 of Each Cycle (±3 days)									Day 1 of Each Cycle (±3 days)	≤30 Days after Final Dose	
	Days –28 to –1	Days –14 to –1	1	2	3	4	5	6	7	8				
Informed consent [f]	x													
Baseline tumor tissue sample [g]	x													
Demographic data	x													
Medical history and baseline conditions	x													
Disease status assessment [h]	x		x	x	x	x	x	x	x	x		x	x	x
Tumor staging [i]	x													
Bilateral mammogram [j]	x												x	x
Surgical treatment plan [k]	x										x			
Pathologic response assessment [l]											x			
Vital signs [m]	x		x	x	x	x	x	x	x	x		x	x	
Weight	x		x	x	x	x	x	x	x	x		x		
Height	x													
Complete physical examination [n]	x									x			x	
Limited physical examination [o]			x	x	x	x	x	x	x			x		

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	Screening/ Baseline [a]		Treatment Cycles										Treatment Discontinuation/Early Termination Visit [d]	Follow-Up [e]
			Neoadjuvant Phase Cycles1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles								Pre-Surgery Visit/ Surgery [b]	Adjuvant Phase [c] (Cycles 9–22) 21-Day Cycles		
			Day 1 of Each Cycle (±3 days)									Day 1 of Each Cycle (±3 days)	≤30 Days after Final Dose	
	Days –28 to –1	Days –14 to –1	1	2	3	4	5	6	7	8				
ECOG Performance Status [p]	x		x				x			x		x	x	
ECHO/MUGA scan [q]	x		See footnote "q"										x	x
ECG (12-lead) [r]	x		As clinically indicated											
Hematology [s]		x [t]	x	x	x	x	x	x	x	x		x	x	
Chemistry [u]		x [t]	x	x	x	x	x	x	x	x		x	x	
Pregnancy test [v]		x	x	x	x	x	x	x	x	x		x	x	x
Coagulation (INR, aPTT)		x [t]								x			x	
TSH, free T3 (or total T3), free T4 [w]	x [t]		x				x					x	x	
HIV, HBV, and HCV serologies	x													
Urinalysis [x]	x		As clinically indicated											
EORTC QLQ-C30, EQ-5D-5L [y]			x	x	x	x	x	x	x	x		x	x	x
FACT-G, single-item GP5 [y, z]				x	x	x	x	x	x	x		x	x	x
Serum autoantibody sample [aa]	x													
PK samples and ADA samples	See Appendix 2 for detailed schedule.													
Blood and plasma sample for biomarkers	See Appendix 3 for detailed schedule.													

Appendix 1: Schedule of Activities

	Screening/ Baseline [a]		Treatment Cycles											
			Neoadjuvant Phase Cycles1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles								Pre-Surgery Visit/ Surgery [b]	Adjuvant Phase [c] (Cycles 9–22) 21-Day Cycles	Treatment Discontinuation/Early Termination Visit [d]	Follow-Up [e]
	Days –28 to –1	Days –14 to –1	Day 1 of Each Cycle (±3 days)									Day 1 of Each Cycle (±3 days)	≤30 Days after Final Dose	
			1	2	3	4	5	6	7	8				
Blood sample for WGS or WES			x											
Whole blood sample types for RBR (optional)			x											
Tumor tissue (fresh sample preferred) at screening, on-study, and at time of disease progression or recurrence	See Appendix 3 for detailed schedule.													
Concomitant medications [bb]		x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [cc]		x	x	x	x	x	x	x	x	x	x	x	x	x
Atezolizumab/placebo administration [dd] Stopped with protocol version 5			x	x	x	x	x	x	x	x		x		
Dose-dense doxorubicin administration [ee]			x	x	x	x								
Dose-dense cyclophosphamide administration [ff]			x	x	x	x								
Pertuzumab administration [gg]							x	x	x	x		x		
Trastuzumab administration [hh]							x	x	x	x		x		

Appendix 1: Schedule of Activities

	Screening/ Baseline [a]		Treatment Cycles										Treatment Discontinuation/Early Termination Visit [d]	Follow-Up [e]
			Neoadjuvant Phase Cycles1–4: 14-Day Cycles Cycles 5–8: 21-Day Cycles								Pre-Surgery Visit/ Surgery [b]	Adjuvant Phase [c] (Cycles 9–22) 21-Day Cycles		
	Days –28 to –1	Days –14 to –1	Day 1 of Each Cycle (±3 days)									Day 1 of Each Cycle (±3 days)	≤30 Days after Final Dose	
			1	2	3	4	5	6	7	8				
Paclitaxel administration [ii]							x	x	x	x				
Trastuzumab emtansine administration [kk]												x		
Survival follow-up and anti-cancer treatment [jj]														x

ADA = anti-drug antibody; AJCC = American Joint Committee on Cancer; CT = computed tomography (scan); ddAC = dose-dense anthracycline (doxorubicin) + cyclophosphamide; ECHO = echocardiogram; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level (questionnaire); FACT-G = Functional Assessment of Cancer Therapy–General; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; MUGA = multiple-gated acquisition (scan); NAST = neoadjuvant systemic therapy; pCR=pathological complete response; PK = pharmacokinetic; PRO = patient-reported outcome; Q3W = every 3 weeks; QLQ-C30 = Quality of Life Questionnaire–Core 30; RBR = Research Biosample Repository; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WES = whole exome sequencing; WGS = whole genome sequencing.

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

[a] Results of SOC tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening.

[b] Pre-surgical visit and associated assessments should occur within 14 days of surgery. Surgery should be conducted no earlier than 14 days and no later than 6 weeks after last dose of neoadjuvant therapy. Platelet counts should be checked prior to surgery and should be ≥75,000 cells/μL.

[c] All study therapy will be completed when the patient has received up to a total duration of 52 weeks of HER2-targeted study therapy (neoadjuvant + adjuvant [i.e., a maximum of 18 cycles of HER2-targeted treatment]).

[d] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit no more than 30 days after their final dose of study treatment or no more than 30 days from the date the decision was made to permanently discontinue study treatment.

[e] The survival follow-up period begins from the date of treatment completion/early termination visit with a duration of 36 months from the date of the enrollment of the last patient. Follow-up visits have a window of ±28 days.

[f] 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.

[g] After signing of the Informed Consent Form, retrieval and submission of tumor tissue sample can occur outside the 28-day screening period. Tumor tissue 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 (preferred) or at least 20 slides containing unstained, freshly cut, serial sections should be provided. Fine-needle aspiration is not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. See Section 4.5.9 for additional details.

[h] Assessment of primary tumor and regional lymph nodes should be done by physical examination at baseline and prior to administration at each cycle of study treatment during neoadjuvant therapy and within 14 days prior to surgery. During the postoperative portion of this study, disease status should be clinically evaluated and documented every 3 months for 2 years, and then every 6 months thereafter until the end of the study. In addition, liver function tests, brain imaging, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease; these assessments should be performed within a timeline as per current local SOC practice. Whenever possible, disease recurrence should be confirmed pathologically. If disease progression or disease recurrence is diagnosed at any time during the study, patients will discontinue study treatment and enter the follow-up phase of the study. Disease status assessments and imaging (mammogram) can be done as per local standard of care for patients with confirmed disease progression or recurrence. All other follow-up assessments apply to patients with disease progression or recurrence as per Schedule of Assessments.

[i] Baseline tumor staging procedures should be performed in alignment with AJCC, 8th edition (specifically in accordance with Anatomic Stage group rules) at diagnosis, within 28 days of randomization. Tumor size is to be determined via radiologic measurement and node positivity pathologically confirmed by fine needle aspiration or core needle biopsy. See Section 4.5.6 for requirements related to baseline distant sites tumor staging procedures.

[j] Bilateral mammogram should be obtained within 28 days prior to randomization. Alternatively, provided that the clinical status of the patients has not changed, the screening mammogram can be performed up to 42 days prior to the start of study treatment. Subsequent mammograms are optional during neoadjuvant treatment and prior to surgery and should be performed per investigator's discretion. Bilateral mammogram should occur at the treatment completion/early termination visit and every 12 months (±4 weeks) during the follow-up period. Patients who have undergone mastectomy do not require mammograms on side of mastectomy. Patients with confirmed disease progression or recurrence can undergo imaging procedures as per local standard of care.

[k] The patient should be evaluated by a surgeon prior to initiation of neoadjuvant therapy as well as after completion of neoadjuvant therapy/prior to surgery. At baseline, the surgeon should evaluate the patient and create a surgical treatment plan. Then, after completion of NAST, the surgeon should reassess the patient and modify the surgical treatment plan as needed.

[l] Pathological response assessment to be performed using the resected specimen by the local pathologist on the basis of guidelines provided in the pathology manual. Breast cancer surgery and pathological assessment will be performed and reported according to protocol requirements for patients who discontinue study treatment during the neoadjuvant phase (for any reason other than disease progression) and who proceed to surgery without receiving any other non-study anti-cancer therapy prior to surgery. Patients who discontinue neoadjuvant study treatment due to disease progression contribute a non-pCR result and their disease progression must be reported.

[m] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to each infusion and, if clinically indicated, every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to each infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during the infusion and at 30 (±10) minutes after the infusion. The vital signs measured prior to the infusion of the first study drug at each cycle are required to be reported on the Vital Sign eCRF. Other vital signs are not required to be entered into the eCRF unless abnormal and clinically significant, in which case they are to be reported as adverse events.

[n] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. See Section 4.5.3 for additional details. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[o] Perform a limited, symptom-directed physical examination at specified timepoints and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[p] See Appendix 13.

[q] Cardiac monitoring (ECHO or MUGA scan) will be performed on all patients enrolled in the study. ECHO/MUGA results need to be reviewed and acted upon as soon as they are available, but study interventions may continue while ECHO/MUGA results are being read assuming that the subject is asymptomatic from a cardiac standpoint. ECHO is the preferred method. The same method used for a given patient at screening should be used throughout the study, unless clinically indicated. ECHO or MUGA scan should be obtained at baseline, after the second dose of ddAC for the cardiac safety cohort (first 26 patients enrolled), after the fourth dose of ddAC (and prior to Cycle 5, Day 1), and then every 3 months (±2 weeks) during study treatment. ECHO or MUGA scan should be obtained at the early termination visit if not performed within the previous 6 weeks. During the survival follow-up period, ECHO or MUGA scan should be obtained every 6 months for the first 2 years and then annually until the end of study. Patients who discontinue study drug(s) for heart failure or LVEF decline should continue to undergo LVEF assessments according to this schedule of activities—irrespective of the initiation of alternative systemic anti-cancer therapy—until resolution, improvement to baseline status, and no further improvement can be expected, or death. Additional ECHO or MUGA scans should be obtained if clinically indicated.

[r] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. ECGs for each patient should be obtained from the same machine wherever possible. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[s] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells). Local laboratory assessment can be performed up to 3 days prior to study treatment administration with the option of repeating on the day of study treatment, including the weekly administration of paclitaxel during Cycles 5–8. Local assessment must be reviewed prior to every study treatment administration.

[t] If screening laboratory assessments were performed within 3 days prior to Day 1 of Cycle 1, they do not have to be repeated.

[u] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, and LDH. Local laboratory assessments can be performed up to 3 days prior to study treatment administration with the option of repeating on the day of study treatment, including the weekly administration of paclitaxel during Cycles 5–8. Local assessments must be reviewed prior to every study treatment administration.

[v] All women of childbearing potential (as defined in Section 4.1.1) will have a serum pregnancy test at screening, within 7 days prior to initiation of study treatment. Urine pregnancy tests will be performed within 24 hours of Day 1 of every cycle until treatment discontinuation. A pregnancy test must be done at the treatment completion/early termination visit, and at 3 months and 7 months after the discontinuation of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[w] 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.

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

[y] The PRO assessments (EORTC QLQ-C30, followed by the FACT-G single item GP5, and then the EQ-5D-5L questionnaire) will 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. In scenarios where laboratory assessments (e.g., blood draws) are done in a different clinic than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PROs as long as results have not been discussed with patients. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. EORTC QLQ-C30 and EQ-5D-5L questionnaires will be completed by patients at baseline (Cycle 1, Day 1); on Day 1 of every cycle thereafter until Cycle 8; on Cycle 9, Day 1; on Day 1 of every other cycle thereafter until Cycle 22; and at the treatment discontinuation/early termination visit. If cycles are missed or delayed as permitted by the protocol, the PRO questionnaires should be completed on the day that the patient receives treatment for that cycle, before administration of study treatment. Patients who discontinue study treatment 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 and then every 6 months (±28 days) thereafter until the end of the study.

[z] While on study treatment, all patients will complete the FACT-G, single item GP5 beginning on Cycle 2, Day 1; on Day 1 of every cycle thereafter until Cycle 8; on Cycle 9, Day 1; on Day 1 of every other cycle thereafter until Cycle 22; and at the treatment discontinuation/early termination visit.

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

[bb] 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 30 days prior to initiation of study treatment (for the purposes of screening) until the treatment discontinuation visit. Medication used by the patient within 7 days prior to initiation of study treatment should be recorded. Record all prior anti-cancer therapies, regardless of when they were received.

[cc] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, 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). For reporting instructions for deaths, please see Section 5.3.5.8.

[dd] During the neoadjuvant phase, atezolizumab/placebo will be administered by IV infusion at a fixed dose of 840 mg on Day 1 of each 14-day cycle during Cycles 1–4, and 1200 mg on Day 1 of each 21-day cycle during Cycles 5–8. During the adjuvant phase (post-operatively), atezolizumab/placebo will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle (maximum of 22 cycles [neoadjuvant + adjuvant phases]). Atezolizumab/placebo should be administered as the first infusion. The initial dose of atezolizumab/placebo 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. See Section 4.3.2.1 for additional details. Following the distribution of the USM DIL dated 3 February 2021, blinded atezolizumab/placebo will no longer be administered to patients.

[ee] Doxorubicin 60 mg/m^2 IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4) according to local practice guidelines. See Section 4.3.2.4 for additional details.

[ff] Cyclophosphamide 600 mg/m^2 IV on Day 1 of a 14-day cycle for 4 cycles (Cycles 1–4) according to local practice guidelines. See Section 4.3.2.4 for additional details.

[gg] Pertuzumab is given as a fixed non–weight-based dose of 840-mg IV loading dose, then 420 mg IV Q3W. Pertuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. Day 1 dose administrations are to be performed within a ±3-day window, unless treatment is delayed or on hold to manage toxicity. If the scheduled dose administration coincides with a holiday that precludes administration, administration should be performed within 7 days following the scheduled date. See Section 4.3.2.2 for additional details.

[hh] Trastuzumab is given as an 8-mg/kg IV loading dose and then 6 mg/kg IV Q3W. Trastuzumab will be administered on Day 1 of a 21-day cycle, to complete up to a total duration of 52 weeks (i.e., maximum of 18 cycles within 1 year) of HER2-targeted therapy, inclusive of therapy given both in the neoadjuvant and adjuvant setting. Day 1 dose administrations are to be performed within a ±3-day window, unless treatment is delayed or on hold to manage toxicity. If the scheduled dose administration coincides with a holiday that precludes administration, administration should be performed within 7 days following the scheduled date. See Section 4.3.2.3 for additional details.

[ii] Paclitaxel is given 80 mg/m^2 IV weekly for 12 continuous weeks (Cycles 5–8) according to local practice guidelines. Chemotherapy should be given after pertuzumab and trastuzumab. See Section 4.3.2.4 for additional details.

[jj] After treatment discontinuation, 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 approximately every 3 months for 1 year, then every 6 months until the end of the study (unless the patient withdraws consent or the Sponsor terminates the study). 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 shall use a public information source (e.g., county records) to obtain information about survival status only, where allowable by local regulation.

[kk] Trastuzumab emtansine will be an option for patients who did not achieve pCR after completion of neoadjuvant treatment. Trastuzumab emtansine will be given as 3.6 mg/kg IV infusion on Day 1 of a 21-day cycle for a maximum of 14 cycles in the adjuvant setting. Day 1 dose administrations are to be performed within a ±3-day window, unless treatment is delayed or on hold to manage toxicity. If the scheduled dose administration coincides with a holiday that precludes administration, administration should be performed within 7 days following the scheduled date. See Section 4.3.2.4 for additional details.

Appendix 2
Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint	Treatment Arms	
		Atezolizumab with ddAC-PacHP	Placebo with ddAC-PacHP
Day 1 of Cycle 1	Prior to the first infusion of atezolizumab/ placebo, pertuzumab, and trasuzumab	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Pertuzumab PK (serum) • Pertuzumab ADA (serum) • Trastuzumab PK (serum) • Trastuzumab ADA (serum)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Pertuzumab PK (serum) • Pertuzumab ADA (serum) • Trastuzumab PK (serum) • Trastuzumab ADA (serum)
	30 (±10) min after end of the atezolizumab/ placebo infusion	• Atezolizumab PK (serum)	• Atezolizumab PK (serum)
Day 1 of Cycles 2, 3, 4, 8, 12, and 16	Prior (within 3 days) to the atezolizumab/ placebo, pertuzumab, and trasuzumab infusions	• Atezolizumab PK (serum) [b] • Atezolizumab ADA (serum) [b] • Pertuzumab PK (serum) (Cycles 8 and 12 only) [a,b] • Pertuzumab ADA (serum) (Cycles 8 and 12 only) [a,b] • Trastuzumab PK (serum) (Cycles 8 and 12 only) [a,b] • Trastuzumab ADA (serum) (Cycles 8 and 12 only) [a,b]	• Atezolizumab PK (serum) [b] • Atezolizumab ADA (serum) [b] • Pertuzumab PK (serum) (Cycles 8 and 12 only) [a,b] • Pertuzumab ADA (serum) (Cycles 8 and 12 only) [a,b] • Trastuzumab PK (serum) (Cycles 8 and 12 only) [a,b] • Trastuzumab ADA (serum) (Cycles 8 and 12 only) [a,b]

Appendix 2: Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint	Treatment Arms	
		Atezolizumab with ddAC-PacHP	Placebo with ddAC-PacHP
Day 1 of Cycle 9	Prior (within 3 days) to the first infusion of trastuzumab emtansine	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • DM1 PK (plasma) [b] • Trastuzumab emtansine ADA (serum)[b]	• Trastuzumab emtansine and total trastuzumab PK (serum)[b] • DM1 PK (plasma) [b] • Trastuzumab emtansine ADA (serum)[b]
	30 (±10) min after the end of the trastuzumab emtansine infusion	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • DM1 PK (plasma) [b]	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • DM1 PK (plasma) [b]
Day 1 of Cycle 12	Prior (within 3 days) to the trastuzumab emtansine infusion	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • Trastuzumab emtansine ADA (serum) [b]	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • Trastuzumab emtansine ADA (serum) [b]
	30 (±10) min after the end of the trastuzumab emtansine infusion	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • DM1 PK (plasma) [b]	• Trastuzumab emtansine and total trastuzumab PK (serum) [b] • DM1 PK (plasma) [b]
Treatment discont. visit (≤30 days after final dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Pertuzumab PK (serum) • Pertuzumab ADA (serum) • Trastuzumab PK (serum) • Trastuzumab ADA (serum) • Trastuzumab emtansine and total trastuzumab PK (serum) • DM1 PK (plasma) • Trastuzumab emtansine ADA (serum)	• Pertuzumab PK (serum) • Pertuzumab ADA (serum) • Trastuzumab PK (serum) • Trastuzumab ADA (serum) • Trastuzumab emtansine and total trastuzumab PK (serum) • DM1 PK (plasma) • Trastuzumab emtansine ADA (serum)

Appendix 2: Schedule of Pharmacokinetic and Immunogenicity Samples

ADA = anti-drug antibody; ddAC-PacHP = dose-dense anthracycline (doxorubicin) + cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; discont. = discontinuation; DM1 = derivative of maytansine; pCR = pathological complete response; PK = pharmacokinetic.

Notes: PK and ADA samples for atezolizumab, pertuzumab, and trastuzumab will be collected for all patients. PK and ADA samples for trastuzumab emtansine will be collected for only those patients receiving trastuzumab emtansine. In an event where a dose is withheld, predose PK and ADA samples should be collected regardless if possible on the day of the planned dose. If more than one dose is withheld, the PK and ADA samples will be handled on a case-by-case basis.

[a] Patients who do not achieve pCR and switch treatment to atezolizumab/placebo with trastuzumab emtansine in the adjuvant phase of the study are not required to provide PK and ADA samples for trastuzumab and pertuzumab at Cycle 12.

[b] Following the discontinuation of atezolizumab or placebo, this sample collection is no longer required. The PK and ADA sample collection for atezolizumab, trastuzumab and pertuzumab (or trastuzumab emtansine) is only required at the treatment discontinuation visit following the implementation of Protocol Version 5.

Appendix 3
Schedule of Blood and Tissue Samples for Biomarker Analysis

Blood Samples

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pretreatment	Plasma sample for biomarkers
		Blood sample for WGS/WES [a, b]
		Whole blood sample for RBR [b, c]
Cycle 2, Day 1	Pretreatment	Plasma sample for biomarkers
Surgery	Pre-surgery	Plasma sample for biomarkers
Cycle 9, Day 1	Pretreatment	Plasma sample for biomarkers
Cycle 13, Day 1	Pretreatment	Plasma sample for biomarkers
Cycle 17, Day 1	Pretreatment	Plasma sample for biomarkers
Treatment discontinuation (≤30 days after final dose) [d]	At any time during visit	Plasma sample for biomarkers
Disease recurrence	At any time during visit	Plasma sample for biomarkers

RBR = Research Biosamle Repository; WES = whole exome sequencing; WGS = whole genome sequencing.

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

[b] If missed on Day 1, this blood sample can be collected at any point in the study.

[c] Not applicable for a site that has not been granted approval for RBR sampling and performed only for patients at participating sites who have provided written optional RBR consent to participate.

[d] If treatment is discontinued due to disease recurrence, the treatment discontinuation sample does not apply and only the disease recurrence sample needs to be collected.

Tissue Samples

Visit	Timepoint	Requirement	Sample Type
Screening [a]	Pre-treatment	Mandatory	A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted. Tumor sample must contain a minimum of 50 viable tumor cells. Samples are to be collected via core-needle biopsy (at least three cores, embedded in a single paraffin block). Fine-needle aspiration is not acceptable. For patients with multifocal tumors, at least one focus must be sampled and centrally confirmed as HER2-positive. A representative FFPE tumor specimen in a paraffin block is preferred or at least 20 slides. Patients with multicentric tumors are eligible provided all discrete lesions are sampled and centrally confirmed as HER2-positive. A representative FFPE tumor specimen in a paraffin block of all lesions is preferred or at least 11 slides are required from each lesion. In addition to this requirement, a total of 9 slides is required for the remaining biomarker tests. Preferably, these additional 9 slides are derived from one lesion.
Surgery		Mandatory	A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted.
Disease recurrence [b]		Mandatory, if clinically feasible	A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted.

FFPE = formalin-fixed, paraffin-embedded; HER2 = human epidermal growth factor 2.

[a] A pretreatment tumor biopsy is required for central eligibility testing. A new pretreatment tumor biopsy may be performed if tissue test results do not meet eligibility criteria. Submission of a tumor sample can occur outside the 28-day screening period. Patients with multicentric tumors are eligible provided all discrete lesions are sampled and centrally confirmed as HER2-positive.

[b] If deemed clinically feasible by the investigator and within 40 days after recurrence or prior to the next anti-cancer therapy, whichever is sooner.

Appendix 4
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	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

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 5
Functional Assessment of Cancer Therapy–General (FACT-G)
Single-Item GP5

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 <u>past 7 days</u>.**

		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 6
EuroQol 5-Dimension, 5-Level Questionnaire: EQ-5D-5L

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

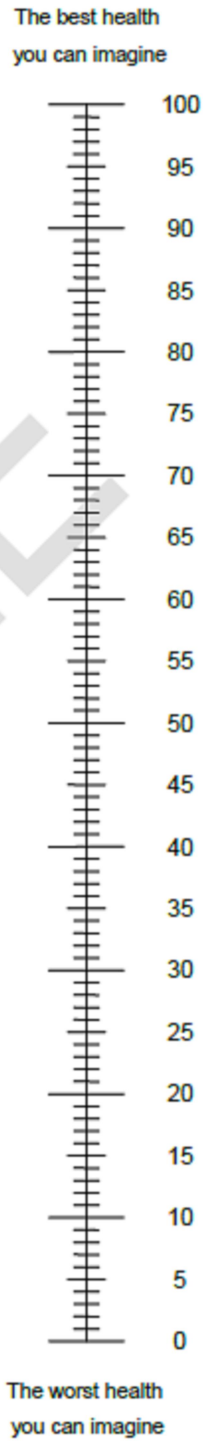
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Appendix 7
Ventana HER2 IHC Assay

The PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody (PATHWAYHER2 [4B5]) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of human epidermal growth factor 2 (HER2) antigen in sections of formalin-fixed, paraffin-embedded breast cancer tissue to determine tumor HER2 immunohistochemistry (IHC) status and to select HER2-positive patients for enrollment in Study BO40747.

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

Appendix 8
Ventana HER2 ISH Assay

Probe Cocktail is intended to determine the ratio of the human epidermal growth factor 2 (HER2) gene to chromosome 17 using two-color chromogenic in situ hybridization (ISH) in formalin-fixed, paraffin-embedded (FFPE) human breast cancer tissue to determine tumor HER2 gene status and select HER2-positive patients for enrollment in Study BO40747.

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

Appendix 9
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

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

Appendix 10
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion.

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 11
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS, TREATMENT INTERRUPTION, AND MANAGEMENT GUIDELINES

When there is a possibility of overlapping toxicities, the attribution of an adverse event to particular drug(s) will be based on the investigator's clinical judgment. See Section 5.1.7 and 5.1.8 for guidance on potential overlapping toxicities.

ATEZOLIZUMAB

On 3 February 2021, the Sponsor issued a USM DIL communicating the request to stop treatment with atezolizumab or placebo.

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

See Appendix 12 for management of adverse events, which are deemed by the investigator, to be due to atezolizumab.

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 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). *T*he 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.*

DOXORUBICIN AND CYCLOPHOSPHAMIDE

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information for doxorubicin and cyclophosphamide, and should be managed as per local practice.

Cardiotoxicity

If severe symptomatic heart failure develops (New York Heart Association [NYHA] Class III or IV) or there is a significant left ventricular ejection fraction (LVEF) decrease (LVEF decline ≥ 10 percentage points from baseline to an LVEF value < 50%), the

patient must discontinue atezolizumab + doxorubicin + cyclophosphamide and not proceed with anti-HER2 therapy. Heart failure or left ventricular dysfunction should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist and the results of this evaluation should be reported on the eCRF.

Patients who discontinue atezolizumab + doxorubicin + cyclophosphamide for heart failure or LVEF decline should continue to undergo LVEF assessments according to the schedule of activities (see Appendix 1)—irrespective of the initiation of alternative systemic anti-cancer therapy—until resolution, improvement to baseline status, no further improvement can be expected, or death. Additional LVEF assessments may be required for these patients (beyond those specified in the schedule of activities), according to the investigator's clinical judgment. The results of these assessments should be reported.

Liver Function

The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of the drug with an increase in overall toxicity. Lower doses are recommended in these patients. Patients with severe hepatic impairment should not receive doxorubicin.

PACLITAXEL

Dose reduction and dose delays will be allowed as indicated in the relevant local prescribing information for paclitaxel, and managed as per local practice.

Pulmonary Events/Pneumonitis

Paclitaxel should be permanently discontinued upon ruling out infectious etiology (using routine microbiological and/or immunologic methods) and making a diagnosis of pneumonitis. After infectious etiology is ruled out, IV high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. The patient will discontinue paclitaxel treatment but may continue receiving other study drugs as per Table 2 below. Also refer to Appendix 12 for atezolizumab-associated pulmonary events.

Refer to the local prescribing information for paclitaxel for further details.

Pertuzumab and Trastuzumab

Pertuzumab and trastuzumab administration may be delayed up to 42 days from the last administered dose to allow resolution of adverse events. If dosing with trastuzumab and

pertuzumab has been delayed for more than 42 days from the last dose and the investigator wishes to restart treatment with trastuzumab and pertuzumab based on a positive benefit–risk assessment for the individual patient, the Medical Monitor is *available for consultation*. For guidance on drug administration requirements related to delayed or missed doses, please see Table 1 below. No dose reduction is permitted for either pertuzumab or trastuzumab. Note that if trastuzumab is permanently discontinued, the patient will not receive adjuvant treatment on study but will enter the study follow-up period.

Table 1 Pertuzumab and Trastuzumab Administration Guidance Regarding Delayed or Missed Doses

Time Between Two Sequential Doses	Pertuzumab	Trastuzumab
$<$6 weeks	The 420-mg dose of pertuzumab IV should be administered as soon as possible. Do not wait until the next planned dose.	The 6 mg/kg dose of trastuzumab IV should be administered as soon as possible. Do not wait until the next planned dose.
$\geq$6 weeks	The loading dose of 840 mg pertuzumab IV should be re-administered as a 60-minute infusion, followed by a maintenance dose of 420 mg IV administered over a period of 30 to 60 minutes every 3 weeks thereafter.	The loading dose of 8 mg/kg of trastuzumab IV should be re-administered over approximately 90 minutes, followed by a maintenance dose of 6 mg/kg IV administered over a period of 30 or 90 minutes every 3 weeks thereafter.

Infusion-Associated Symptoms

If infusion-associated symptoms occur, patients should be monitored until complete resolution of signs and symptoms. Patients who experience infusion-associated symptoms may be managed by slowing or interrupting the infusion and by providing supportive care with oxygen and medications (e.g., β-agonists, antihistamines, antipyretics, or corticosteroids), as determined by the investigator to be clinically appropriate. Patients who experience infusion-associated symptoms may subsequently be premedicated with analgesia and antihistamines. If the infusion is well tolerated, patients will be observed for 30 minutes following subsequent infusions. The infusion of pertuzumab or trastuzumab should be stopped in patients who develop dyspnea or clinically significant hypotension (defined as per investigator discretion). Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction or acute respiratory distress syndrome should be discontinued from treatment.

Cardiotoxicity

If severe symptomatic heart failure develops (NYHA Class III or IV), the patient must discontinue anti-HER2 therapy. If there is a significant LVEF decrease (LVEF decline $\geq$10 percentage points from baseline to an LVEF value $<$50%) anti-HER2 therapy should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further or if clinically significant heart failure develops, the patient must discontinue anti-HER2 therapy. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6–8 weeks). Heart failure or left ventricular dysfunction should be treated and monitored according to standard medical practice. These patients should be evaluated by a certified cardiologist and the results of this evaluation should be reported on the eCRF.

Patients who discontinue anti-HER2 therapy for heart failure or LVEF decline should continue to undergo LVEF assessments according to the schedule of activities (Appendix 1)—irrespective of the initiation of alternative systemic anti-cancer therapy—until resolution, improvement to baseline status, no further improvement can be expected, or death. Additional LVEF assessments may be required for these patients (beyond those specified in the schedule of activities), according to the investigator's clinical judgment. The results of these assessments should be reported.

Pulmonary Toxicity

Severe pulmonary events have been reported with the use of the trastuzumab IV formulation in the postmarketing setting. These events have occasionally been fatal. They may occur as part of an IRR or with delayed onset. In addition, cases of interstitial lung disease, including lung infiltrates, acute respiratory distress syndrome (ARDS), pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and respiratory insufficiency have been reported with trastuzumab IV. These events have been most common with the first infusion, and their severity has decreased with subsequent infusions. Serious reactions have been treated successfully with supportive therapy, such as oxygen, β-agonists, and corticosteroids. ARDS has been reported with a fatal outcome.

Refer to the Trastuzumab Investigator's Brochure and Pertuzumab Investigator's Brochure for the most recent data related to the associated risks.

Epidermal Growth Factor Receptor (EGFR)–Related Toxicities

To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered, and patients should be treated with fluids and electrolyte replacement, as clinically indicated.

Treatment recommendations for EGFR-associated rash include topical or oral antibiotics, and topical steroids or systemic steroids (for severe reactions).

These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated, although they have not been studied in this context.

Mucositis is generally not considered preventable; although for some cytotoxic agents, mucositis may be reduced by cooling the mouth using ice chips before and during the infusion.

MODIFICATIONS OF STUDY TREATMENT REGIMEN IF AGENT(S) CANNOT BE ADMINISTERED (IN THE EVENT OF TOXICITY)

Investigators *may consult with* the Medical Monitor before discontinuing all components of study treatment. See Table 2, Table 3, and Table 4 for modifications of study treatment regimen in the event that agent(s) cannot be administered (e.g., due to toxicity).

Table 2 Neoadjuvant Cycles 1–4: Atezolizumab/Placebo and Dose-Dense (dd) Doxorubicin (A) + Cyclophosphamide (C)

Regimen	Unable to Administer within 14 Days of Scheduled Dosing (i.e., Cycle X, D1 + 14 Days)	Action
Atezolizumab/ Placebo + ddAC	Either A or C	Do not continue with only one component of the chemotherapy backbone. Move to 4 cycles of atezolizumab/placebo + PacHP. Per investigator discretion: Option to make up missed chemotherapy cycles post-surgery and prior to adjuvant therapy with atezolizumab/placebo + HP. Note: Due to increased risk of cardiotoxicity, ddAC is NOT to be given within 21 days of prior H and/or P.[b] ddAC is NOT to be given concurrently with H and/or P.
	ddAC	Move to 4 cycles atezolizumab/placebo + PacHP. Per investigator discretion: Option to make up missed chemotherapy cycles post-surgery and prior to adjuvant therapy with atezolizumab/placebo + HP. Note: Due to increased risk of cardiotoxicity, ddAC is NOT to be given within 21 days of prior H and/or P.[b] ddAC is NOT to be given concurrently with H and/or P.
	Atezolizumab/placebo	Continue ddAC then switch to PacHP followed by surgery followed by > HP adjuvant therapy. Atezolizumab/placebo may be reintroduced with subsequent cycles of therapy[a] if criteria for restarting are met. (See above in Appendix 11 and also Appendix 12, Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab.)

A = doxorubicin; C = cyclophosphamide; D1 = Day 1; dd = dose-dense; ddAC = dose-dense anthracycline (doxorubicin) + cyclophosphamide; H = trastuzumab; P = pertuzumab; PacHP = paclitaxel + trastuzumab + pertuzumab.

[a] When atezolizumab is restarted, the infusions should remain synchronized and aligned with the chemotherapy schedule.

[b] The only exception is the period between Cycle 4 and Cycle 5 during which the Cycle 4 ddAC administration will be given 14 days prior to the Cycle 5 administration of HP.

Table 3 Neoadjuvant Cycles 5–8: Atezolizumab/Placebo and Paclitaxel + Trastuzumab + Pertuzumab (PacHP)

Regimen	Unable to Administer	Action	Impact on Adjuvant (Post-Operative) Treatment
If 1 agent in the regimen cannot be administered (i.e., due to toxicity) within 21 days of scheduled dosing (i.e., Cycle X, D1 + 21 days)			
Atezolizumab/ Placebo + PacHP	Atezolizumab/placebo	Continue PacHP. Atezolizumab/placebo may be reintroduced with subsequent cycles of therapy [a] if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety, and Appendix 12, Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab.)	HP adjuvant treatment. Atezolizumab/placebo may be reintroduced with subsequent cycles of therapy [a] if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety, and Appendix 12, Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab.)
	Pertuzumab (P)	Continue atezolizumab/ placebo ± PacH. Pertuzumab may be reintroduced with subsequent cycles of therapy [a] if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety.)	Pertuzumab may be reintroduced with subsequent cycles of therapy [a] if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety.)
	Trastuzumab (H)	Continue Atezolizumab/ Placebo + PacP. Trastuzumab may be reintroduced with subsequent cycles of therapy [a] if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety.)	If H is permanently discontinued, no further adjuvant treatment (no H, P or atezolizumab/ placebo). Patient enters study follow-up.

Table 3 Neoadjuvant Cycles 5–8: Atezolizumab/Placebo and Paclitaxel + Trastuzumab + Pertuzumab (PacHP) (cont.)

Regimen	Unable to Administer	Action	Impact on Adjuvant (Post-Operative) Treatment
	Paclitaxel (Pac) [b]	Per investigator discretion, either: (1) Proceed to surgery. (2) Continue atezolizumab/ placebo + HP. Paclitaxel (Pac) may be reintroduced with subsequent cycles of therapy [a] if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety.)	Per investigator discretion: Option to make up missing chemotherapy cycle(s) post-surgery followed by atezolizumab/ placebo + HP adjuvant treatment. (Per investigator discretion: HP and atezolizumab/placebo may be added to post-surgery chemotherapy.)
If 2 agents in the regimen cannot be administered (i.e., due to toxicity) within 21 days of scheduled dosing (i.e., Cycle X, D1 + 21 days)			
Atezolizumab/ Placebo + PacHP	Pac + H Pac + P H + P	Proceed to surgery. Postoperatively, per investigator discretion option to make up missing Pac + H + P + atezolizumab/placebo, followed by adjuvant H + P + atezolizumab/placebo if criteria for restarting agent(s) are met. (See above in Appendix 11 and also Section 5, Assessment of Safety, and Appendix 12, Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab.) If two or more of Pac, H, or P have been permanently discontinued then the patient stops all study therapies and enters follow up.	

D1 = Day 1; H = trastuzumab; P = pertuzumab; Pac = paclitaxel; PacHP = paclitaxel + trastuzumab + pertuzumab.

[a] When agent is restarted, the infusions should remain synchronized and aligned with the treatment schedule.

[b] Patients may continue atezolizumab/placebo + HP during periods of chemotherapy-induced myelosuppression (e.g., chemotherapy may be delayed but H/P/atezolizumab/placebo are given while blood counts are waiting to recover) but should be carefully monitored for complications of neutropenia.

Table 4 Adjuvant Cycles 9–22: Atezolizumab/Placebo and Trastuzumab+Pertuzumab (HP) or Atezolizumab/Placebo and Trastuzumab Emtansine

Regimen	Unable to Administer within 21 Days of Scheduled Dosing (i.e., Cycle X D1+21 Days)	Action
Atezolizumab/ Placebo+ HP	Atezolizumab/placebo	Continue HP. Atezolizumab/placebo may be reintroduced with subsequent cycles of therapy if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety, and Appendix 12, Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab.)
	Pertuzumab (P)	Continue atezolizumab/placebo+H. Pertuzumab may be reintroduced with subsequent cycles of therapy if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety.)
	Trastuzumab (H)	Per investigator discretion, may either: (1) Hold all agents. (2) Continue atezolizumab±P. Trastuzumab may be reintroduced with subsequent cycles of therapy if criteria for restarting are met. (See above in Appendix 11 and also Section 5, Assessment of Safety.) If/when trastuzumab is permanently discontinued, then discontinue all components of the regimen and move to follow up.

Table 4 Adjuvant Cycles 9–22: Atezolizumab/Placebo and Trastuzumab+Pertuzumab (HP) or Atezolizumab/Placebo and Trastuzumab Emtansine (cont.)

Regimen	Unable to Administer within 21 Days of Scheduled Dosing (i.e., Cycle X, D1+ 21 Days)	Action
Atezolizumab/ Placebo + Trastuzumab Emtansine	Atezolizumab/placebo	Continue trastuzumab emtansine. Atezolizumab/placebo may be reintroduced with subsequent cycles of therapy if criteria for restarting are met.
	Trastuzumab emtansine	Hold all agents. Trastuzumab emtansine (with atezolizumab/placebo) may be reintroduced with subsequent cycles of therapy if criteria for re-starting are met. (See Section 5.1.6, Section 5.1.10.1, Appendix 14, and Appendix 15) If trastuzumab emtansine is permanently discontinued for toxicity not considered related to the trastuzumab component of the drug, treatment can be switched to trastuzumab and pertuzumab with atezolizumab/placebo to complete a total of 1 year of HER2-targeted therapy.

D1 = Day 1; H = trastuzumab; P = pertuzumab.

Notes: All study therapy will be completed following 52 weeks of HER2-targeted therapy (neoadjuvant + adjuvant), regardless of the number of cycles administered.

Following the distribution of the USM DIL dated 3 February 2021, patients will no longer receive atezolizumab or placebo.

Appendix 12
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

When there is a possibility of overlapping toxicities, the attribution of an adverse event to particular drug(s) will be based on the investigator's clinical judgment. See Section 5.1.7 and 5.1.8, and Appendix 11 for guidance on potential overlapping toxicities.

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 a given patient may be experiencing prior to further administration of atezolizumab. Resumption of atezolizumab may be considered *in* patient*s who are* deriving benefit and ha*ve* 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*.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed as clinically indicated.

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. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*

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 p*atients 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.*

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c, d] • 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] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with 1–2 mg/kg/day *IV methylprednisolone*. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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 p*atients 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.*

[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. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

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 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 p*atients 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 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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 benefitrisk 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 p*atients 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. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended. • 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.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

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 p*atients 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 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] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • 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.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmat*ory* biopsy. • 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. • 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 p*atients 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.*

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. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Grade 2 hypothyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*

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-related event. *The decision to re-challenege p*atients 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 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • *R*efer to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH <0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • *Consider patient referral to endocrinologist.*

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-related event. *The decision to re-challenege p*atients 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 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 2 hyperthyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug*s* such as methimazole or carbimazole as needed. • *R*efer to *an* endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact *the* Medical Monitor for life-threatening immune-mediated hyperthyroidism.[c]

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-related event. *The decision to re-challenege p*atients 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 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • 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 resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • *Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.* • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

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 *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 p*atients 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 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] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • 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. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 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 p*atients 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. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • 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 p*atients 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 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD*, or pericardiocentesis* as appropriate. • Initiate treatment with 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. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS AND CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretic *medications*, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or

other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Riegler 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, including atezolizumab (Rotz et al. 2017; Adashek and Feldman 2019).

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 medical management of IRRs and CRS during Cycle 1 are provided in Table 7.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include 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 COVID-19 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 1a Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS ($>$2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic $medications$, and/or analgesics, and monitor closely for IRRs and/or CRS.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

Event	Management
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic *medications*, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact *the* Medical Monitor.

Table 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] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4a Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor.[e] • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 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: These management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive antipyretic *medications*, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic *medications*, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge p*atients 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 workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	Amylase and/or lipase $>1.5–2.0\times$ ULN: • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Asymptomatic with amylase and/or lipase $>2.0–5.0\times$ ULN: • 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] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

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 p*atients 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 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 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 resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 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. • 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 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 p*atients with atezolizumab *should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. 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. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*

[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 p*atients with atezolizumab *should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤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 p*atients with atezolizumab *should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 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. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology *and refer patient to neurologist*. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab.* [b] – *If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]

[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 p*atients 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 10 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • 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 p*atients 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.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including but not limited to headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to neurologist. • Initiate treatment with 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. • 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. • Monitor kidney function, including creatinine *and urine protein*, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge p*atients 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. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact *the* Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

[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 p*atients 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 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. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the Medical Monitor.* [c]

[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 by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge p*atients 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 14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on the investigator's benefit–risk assessment by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge p*atients with atezolizumab *should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed*.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 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. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact *the* Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 13
Eastern Cooperative Oncology Group
Scale of Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix 14
Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine

Guidelines for managing specific adverse events are provided in the table below. For adverse events not listed in the table, the following guidance should be used: for Grade 3 non-hematologic adverse events not adequately managed by standard medical intervention or for any Grade 4 non-hematologic adverse event, study treatment should be held until recovery to Grade ≤ 1. A maximum dose delay of 42 days from the last administered dose of study drug will be allowed for recovery. After appropriate recovery, trastuzumab emtansine may be resumed with one dose level reduction (e.g., trastuzumab emtansine reduced from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg). For patients who have an event while being treated with trastuzumab emtansine 2.4 mg/kg, trastuzumab emtansine will be discontinued. The dose of trastuzumab emtansine, once reduced, may not be re-escalated.

Appendix 14: Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine

Table 1 Guidelines for Managing Specific Adverse Events

Event	Action to Be Taken
Infusion reactions (caused by cytokine release)/Hypersensitivity (allergic reactions)	
Life threatening infusion-related reaction/ Hypersensitivity (allergic reaction)	Stop infusion, study treatment permanently discontinued. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used, as appropriate, at the investigator's discretion. Patients should be monitored until complete resolution of symptoms.
Infusion-related or clinically significant hypotension	Stop infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patients until complete resolution of symptoms. May re-treat at investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.
Infusion-related symptoms (e.g., chills, fever)	Decrease infusion rate by 50% or interrupt infusion for patients who experience any other infusion-related symptoms (e.g., chills, fever). When symptoms have completely resolved, infusion may be restarted at ≤50% of prior rate and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate at the next cycle, with appropriate monitoring. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used as appropriate at the investigator's discretion. Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent infusions at the investigator's discretion. Patients should be monitored until complete resolution of symptoms.
Hematologic toxicity	
Grade ≥3 hematologic toxicity (other than thrombocytopenia)	Withhold study treatment until recovery to Grade ≤1. Weekly CBC assessments should be performed until recovery, or as medically indicated. A maximum dose delay of 42 days from the last administered dose to Grade ≤1 or baseline will be allowed; otherwise, patients must be discontinued from study treatment.

Appendix 14: Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine

Table 1 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
Hematologic toxicity (cont.)	
Grade 2 or 3 thrombocytopenia on day of scheduled treatment	Assess platelet counts weekly or as medically indicated until recovery. Hold trastuzumab emtansine treatment until Grade ≤1. Resume treatment without dose reduction. If a patient requires two delays due to thrombocytopenia, consider reducing dose by one level.
Grade 4 thrombocytopenia at any time	Assess platelet counts weekly or as medically indicated until recovery. Hold trastuzumab emtansine until Grade ≤1, then resume with one dose level reduction (i.e., from 3.6 mg/kg to 3 mg/kg or from 3 mg/kg to 2.4 mg/kg) in subsequent cycles. If event occurs with 2.4 mg/kg dose, discontinue study treatment.
Hepatotoxicity	
ALT	For a Grade 2 or 3 ALT increase that occurs on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until ALT recovers to Grade ≤1. Resume with dose reduction by one level for Grade 2 or 3 elevations. Grade 2 or 3 ALT elevations that are noted between cycles do not require dose delay or reduction unless ALT remains elevated (Grade ≥2) at the time of planned dosing. For Grade 4 ALT increase, discontinue trastuzumab emtansine. Repeat laboratory evaluation (within 24 hours) may be performed to exclude laboratory error prior to discontinuing study treatment.
AST	For Grade 2 AST increase on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until AST recovers to Grade ≤1. Resume without dose reduction when recovered. For Grade 3 AST increase on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until AST recovers to Grade ≤1. Resume with dose reduction by one level when recovered. For Grade 4 AST increase, discontinue trastuzumab emtansine. Repeat laboratory evaluation (within 24 hours) may be performed to exclude laboratory error prior to discontinuing study treatment.

Appendix 14: Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine

Table 1 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
Hepatotoxicity (cont.)	
TBILI	For TBILI $>1.0\times$ ULN to $\leq 2.0\times$ ULN that occurs on the laboratory evaluation for cycle Day 1 or the day of planned dosing, hold trastuzumab emtansine until TBILI recovers to $\leq 1.0\times$ ULN (or direct bilirubin recovers to $\leq 1.0\times$ ULN for patients with Gilbert's syndrome). For TBILI elevations $>1.0\times$ ULN to $\leq 2.0\times$ ULN, resume when recovered with a one level dose reduction. For TBILI $>2\times$ ULN at any time (or direct bilirubin $>2\times$ ULN for Gilbert's syndrome), discontinue trastuzumab emtansine and report the event as an serious adverse event (if applicable) or non-serious expedited adverse event (if applicable). Assess AST, ALT, and TBILI weekly or as medically indicated until recovery. Allow a maximum dose delay of 42 days from the last administered dose to recovery as described above or otherwise discontinue study treatment.
Nodular Regenerative Hyperplasia	For any clinical signs of liver dysfunction, discontinue trastuzumab emtansine and have the patient evaluated by a hepatologist. If there are signs of portal hypertension (e.g., ascites and/or varices) and a cirrhosis-like pattern is seen on CT scan of the liver, the possibility of NRH should be considered. Trastuzumab emtansine should be discontinued in the event of a diagnosis of NRH.
Neurotoxicity	
Grade ≥ 3 peripheral neuropathy	Discontinue trastuzumab emtansine if event does not resolve to Grade ≤ 2 or baseline value within 42 days after the last administered dose.
Cardiotoxicity	
LVSD	See Figure 3 for the algorithm for continuation and discontinuation of study treatment on the basis of asymptomatic LVEF assessment.
Grade 3 or 4 LVSD or Grade 3 or 4 heart failure	Discontinue study treatment.

Appendix 14: Guidelines for Management of Adverse Events Associated with Trastuzumab Emtansine

Table 1 Guidelines for Managing Specific Adverse Events (cont.)

Event	Action to Be Taken
Cardiotoxicity (cont.)	
Grade 2 heart failure accompanied by LVEF < 45%	Discontinue study treatment.
Interstitial lung disease	
Grade 3 or 4 pneumonitis	Discontinue study treatment regardless of attribution.
Grade 1 or 2 pneumonitis	Discontinue study treatment if not radiotherapy-related. For symptomatic (Grade 2) radiotherapy-related pneumonitis, discontinue if not resolving with standard treatment (e.g., steroids). Relationship to radiotherapy should be determined on the basis of timing and location of radiographic abnormalities relative to the radiation treatment. Upon diagnosis of drug-related ILD/pneumonitis, trastuzumab emtansine treatment has to be permanently discontinued.
	Patients discontinued from trastuzumab emtansine for pneumonitis may not switch study treatment to trastuzumab and pertuzumab and have to discontinue all study treatment.
Radiotherapy-related skin toxicity	
Grade 3 or 4	Do not administer study treatment until recovery to Grade ≤ 1.

CBC = complete blood count; CT = computed tomography; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; NRH = nodular regenerative hyperplasia; ULN = upper limit of normal.

Appendix 15
Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

The following adverse events are potential overlapping toxicities associated with combination use of trastuzumab emtansine and atezolizumab: pulmonary and hepatic events. If trastuzumab emtansine is held for toxicity, then atezolizumab/placebo must also be held. If trastuzumab emtansine is discontinued for toxicity, atezolizumab/placebo must not be continued as single agent and must either be discontinued also or may be continued in combination with trastuzumab and pertuzumab to complete a total of 1 year of HER2-targeted therapy if the investigator considers the toxicity to be related to trastuzumab emtansine without compromising the continued use of trastuzumab. If treatment with atezolizumab/placebo had been discontinued prior to the discontinuation of trastuzumab emtansine or if both treatments are discontinued concurrently, it is at the investigator's discretion to switch treatment to trastuzumab and pertuzumab if the toxicity is not considered related to the trastuzumab component of trastuzumab emtansine.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary infiltrates and have primarily been observed in patients with underlying non–small cell lung cancer.

Mild to moderate events of pneumonitis have been reported with atezolizumab.
All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (diffusion capacity of the lung for carbon monoxide)
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study.
COVID-19 evaluation should be performed per institutional guidelines where relevant.
See Table 1 for management guidelines for pulmonary events and pneumonitis.

Appendix 15: Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

Table 1 Management Guidelines for Interstitial Lung Disease and Pneumonitis

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
Grade 1 or 2	Grade 2: withhold treatment and initiate corticosteroids if radiotherapy-related. If not radiotherapy-related, discontinue all study treatment.	Discontinue all study treatment if not radiotherapy-related. For symptomatic (Grade 2) radiotherapy-related pneumonitis, discontinue if not resolving with standard treatment (e.g., steroids).
Grade 3 or 4	Discontinue atezolizumab/placebo treatment.	Discontinue trastuzumab emtansine treatment.

Note: Patients discontinued from trastuzumab emtansine for pneumonitis may not switch study treatment to trastuzumab and pertuzumab and have to discontinue all study treatment.

HEPATIC EVENTS

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Liver function will be monitored throughout study treatment.

While in this study, patients who present with right upper quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

If outcome of LFTs is worsening, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for worsening outcome of LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti–smooth muscle antibody tests should be performed if an autoimmune etiology is considered. See Table 2 for management guidelines for increased transaminases (AST/ALT) and hepatic events. See Table 3 for dose modifications of trastuzumab emtansine for hyperbilirubinemia. Note: No dose modification for atezolizumab/placebo is indicated on the basis of hyperbilirubinemia alone.

Appendix 15: Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

Table 2 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
ALT or AST increase that meets Hy's Law criteria: ALT or AST $>3\times$ ULN in combination with TBILI $>2\times$ ULN or clinical jaundice	Discontinue atezolizumab/placebo treatment.	Discontinue trastuzumab emtansine treatment.
ALT/AST Grade 2 ($>3.0–5.0\times$ ULN)	Withhold atezolizumab/placebo dose. If persists $>5–7$ days: Consider starting 1–2 mg/kg/day prednisone or equivalent per day; when recovered to Grade ≤ 1, taper steroids over ≥ 1 month. Resume therapy when systemic steroid dose is $\leq$ 10mg oral prednisone equivalent per day and when recovered to Grade ≤ 1 within 12 weeks. Permanently discontinue atezolizumab/placebo and contact the Medical Monitor if event does not resolve to Grade ≤ 1 within 12 weeks.	Withhold trastuzumab emtansine dose until recovery to Grade ≤ 1. Resume with dose reduction by one level when recovered from Grade 2 ALT elevation. No dose reduction needed after recovery from Grade 2 AST elevation.
ALT/AST Grade 3 ($>5.0–20.0\times$ ULN)	Discontinue atezolizumab/placebo treatment. Consider *patient referral to gastrointestinal specialist for evaluation* and liver biopsy to establish etiology of hepatic injury if necessary. Start 60 mg prednisone or equivalent per day. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1.	Withhold trastuzumab emtansine dose until recovery to Grade ≤ 1. Resume with dose reduction by one level when recovered.

Appendix 15: Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

Table 2 Management Guidelines for Increased Transaminases (AST/ALT) and Hepatic Events (cont.)

Severity	Atezolizumab/Placebo	Trastuzumab Emtansine
ALT/AST Grade 4 ($> 20.0 \times$ ULN)	Discontinue atezolizumab/placebo treatment. Consider *patient referral to gastrointestinal specialist for evaluation* and liver biopsy to establish etiology of hepatic injury if necessary. Start 60 mg prednisone or equivalent per day. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) may be considered. Taper steroids over ≥ 1 month, when symptoms improve to Grade 0 or Grade 1.	Discontinue trastuzumab emtansine treatment. Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.
NRH If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered.	Discontinue atezolizumab/placebo treatment.	For any clinical signs of liver dysfunction, discontinue trastuzumab emtansine and have the patient evaluated by a hepatologist. If there are signs of portal hypertension (e.g., ascites and/or varices) and a cirrhosis-like pattern is seen on CT scan of the liver, the possibility of NRH should be considered. Trastuzumab emtansine should be discontinued in the event of a diagnosis of NRH.

CT = computed tomography; GI = gastrointestinal; LFT = liver function test; NRH = Nodular Regenerative Hyperplasia; TNF = tumor necrosis factor; ULN = upper limit of normal.

Appendix 15: Guidelines for Management of Adverse Events that are Potential Overlapping Toxicities Associated with Trastuzumab Emtansine in Combination with Atezolizumab

Table 3 Trastuzumab Emtansine Dose Modification Guidelines for Hyperbilirubinemia

Event	Action to be Taken
TBILI	For TBILI $> 1.0 \times$ ULN to $\leq 2.0 \times$ ULN that occurs on the laboratory evaluation for cycle Day 1 or the day of planned dosing, hold trastuzumab emtansine until TBILI recovers to $\leq 1.0 \times$ ULN (or direct bilirubin recovers to $\leq 1.0 \times$ ULN for patients with Gilbert's syndrome). For TBILI elevations $> 1.0 \times$ ULN to $\leq 2.0 \times$ ULN, resume when recovered with a one level dose reduction. For TBILI $> 2 \times$ ULN at any time (or direct bilirubin $> 2 \times$ ULN for Gilbert's syndrome), discontinue trastuzumab emtansine and report the event as an serious adverse event (if applicable) or non-serious expedited adverse event (if applicable). Assess AST, ALT, and TBILI weekly or as medically indicated until recovery. Allow a maximum dose delay of 42 days from the last administered dose to recovery as described above or otherwise discontinue study treatment.

ULN = upper limit of normal.

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