Official Title: My Pathway: An Open-Label Phase IIA Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, Vismodegib, Alectinib, and Atezolizumab in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

NCT Number: NCT02091141

Document Date: Protocol Version 12: 17-December-2022

PROTOCOL

TITLE:	**MY PATHWAY: AN OPEN-LABEL PHASE IIA STUDY EVALUATING TRASTUZUMAB/PERTUZUMAB, ERLOTINIB, VEMURAFENIB/COBIMETINIB, VISMODEGIB, ALECTINIB, AND ATEZOLIZUMAB IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH MUTATIONS OR GENE EXPRESSION ABNORMALITIES PREDICTIVE OF RESPONSE TO ONE OF THESE AGENTS**
PROTOCOL NUMBER:	ML28897/PRO 02
VERSION NUMBER:	12
Eudract Number:	Not applicable
IND NUMBER:	118664
TEST PRODUCTS:	Trastuzumab plus Pertuzumab; Erlotinib; Vemurafenib plus Cobimetinib; Vismodegib; Alectinib; Atezolizumab
SPONSOR:	Genentech, Inc.
APPROVAL:	*See electronic signature and date stamp on the final page of this document.*

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
12	*See electronic date stamp on the final page of this document*
11	*19 January 2022*
10	22 February 2021
9	27 April 2020
8	07 November 2019
7	26 July 2019
6	29 August 2018
5	14 May 2018
4	6 February 2017
3	5 May 2016
2	11 November 2014
1	15 January 2014

PROTOCOL AMENDMENT, VERSION 12: RATIONALE

Protocol ML28897 has been amended primarily to update safety information for atezolizumab and to remove survival follow-up. Changes to the protocol, along with a rationale for each change, are summarized below:

General Updates

- Atezolizumab approval information has been updated (Sections 1.2.6 and 3.1).
- The study schema has been updated to reflect current enrollment status (Figure 1).
- Coronavirus disease 19 (COVID-19) benefit-risk information and guidance for COVID-19 vaccination has been expanded upon to include active treatment cohorts that are non-immunotherapy treatments (i.e. trastuzumab plus pertuzumab). Due to these updates, some language from the atezolizumab COVID benefit-risk section was removed due to rendundancy (Sections 1.4.1, 1.4.2 and 4.4.1).
- Due to the maturity of the study and to reduce burden on patients and sites, the post-treatment follow-up period has been removed from the study (survival follow-up and progression-free survival follow-up). Language has been updated in the main body and the appendices for all currently active cohorts (Sections 3.2, 4.5.5, 4.6, 4.6.1, 5.3.5.7, and Appendix 6 – Section A6-4.5.5 and A6-Table 3, Appendix 8 – Section A8-4.5.6 and A8-Table 4, Appendix 11 – Section A11-4.5.5 and A11-Table 3).
- 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 in Section 5.4.1 has been replaced with a sentence indicating that this information will be provided separately to sites.
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Clinical Trials Regulation requirements (Section 8.4).
- The URL for the Roche Global Policy on Sharing of Clinical Study Information has been updated (Section 9.5).
- Text has been modified to clarify that summaries of clinical study results may be available for public access in health authority databases (Section 9.5).

Trastuzumab plus Pertuzumab-specific Updates

- To reduce burden on patients and sites, tumor assessment frequency has been reduced and is now to be performed as clinically indicated since the study has met the primary endpoint of overall response rate (ORR) and patients have already been on study treatment for a considerable duration. Language regarding submission of scans to an Independent Review Committee has been removed as it is no longer applicable (Appendix 6 – Sections A6-4.5.3, A6-4.5.4, and A6-Table 3). For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles (Appendix 6 – Section A6-4.5.4 and A6-Table 3).

- To reduce patient burden, a plasma sample for biomarkers at the end of treatment visit is no longer required (Appendix 6 – Section A6-4.5.4 and A6-Table 3).

Atezolizumab-specific Updates

- To reduce burden on patients and sites, tumor assessment frequency has been reduced to every 6 cycles or when clinically indicated and scans will no longer be evaluated by the Independent Review Committee since the study has met the primary endpoint of ORR and patients have already been on study treatment for a considerable duration (Sections 4.5.1.3, 4.5.4, 6.1, 6.2.1, and Appendix 11 – Sections A11-4.3, A11-4.5.3, A11-4.5.4, and A11-Table 3). For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles (Appendix 11 – Section A11-4.5.4 and A11-Table 3).
- To reduce burden, patient-reported outcomes will no longer be required (Appendix 11 – Sections A11-4.5.1.1, A11-4.5.3, A11-4.5.4, and A11-Table 3).
- Pregnancy testing after the end-of-treatment visit is no longer required per standard atezolizumab guidance (Appendix 11 – A11-Table 3).
- The list of identified risks for atezolizumab has been revised to include pericardial disorders, facial paresis, and myelitis (Appendix 11 – Section A11-4.3.1).
- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab, and language has been revised accordingly (Appendix 11 – Section A11-4.3.1).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (Section 5.2.3).
- Appendix 11 –Table 1 has been revised to include autoimmune myelitis.
- Appendix 13 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti-cancer agent.
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19 and Addendum 2 to the Atezolizumab Investigator's Brochure, Version 19 (Appendix 13).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**MY PATHWAY: AN OPEN-LABEL PHASE IIA STUDY EVALUATING TRASTUZUMAB/PERTUZUMAB, ERLOTINIB, VEMURAFENIB/COBIMETINIB, VISMODEGIB, ALECTINIB, AND ATEZOLIZUMAB IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH MUTATIONS OR GENE EXPRESSION ABNORMALITIES PREDICTIVE OF RESPONSE TO ONE OF THESE AGENTS**
PROTOCOL NUMBER:	ML28897/PRO 02
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SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form as instructed by the contract research organization (CRO). Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**MY PATHWAY: AN OPEN-LABEL PHASE IIA STUDY EVALUATING TRASTUZUMAB/PERTUZUMAB, ERLOTINIB, VEMURAFENIB/COBIMETINIB, VISMODEGIB, ALECTINIB, AND ATEZOLIZUMAB IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH MUTATIONS OR GENE EXPRESSION ABNORMALITIES PREDICTIVE OF RESPONSE TO ONE OF THESE AGENTS**
PROTOCOL NUMBER:	ML28897/PRO 02
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IND NUMBER:	118664
TEST PRODUCTS:	Trastuzumab plus Pertuzumab; Erlotinib; Vemurafenib plus Cobimetinib; Vismodegib; Alectinib; Atezolizumab
PHASE:	IIa
INDICATION:	Solid Tumors
SPONSOR:	Genentech, Inc.

Objectives

Primary Objective

The primary objective for this study is to evaluate the efficacy of trastuzumab plus pertuzumab, erlotinib, vemurafenib plus cobimetinib, vismodegib, alectinib, and atezolizumab in patients with advanced solid tumors and: 1) with molecular alterations (mutations, gene expression abnormalities, elevated tumor mutational burden) predictive of response to one of these agents, 2) with no prior approved indication for use of these agents, and 3) for whom therapies that will convey clinical benefit are not available and/or are not suitable options per the treating physician's judgment.

Secondary Objectives

The secondary objectives for this study are as follows:

- To evaluate the safety and tolerability of the study medications for the tumor types studied
- To collect and store molecular profiling data of all patients treated in this study, for the purpose of correlating treatment response with patterns of tumor genetic abnormalities

Exploratory Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- All disease cohorts: to evaluate the association of the levels and nature of somatic tumor-specific mutations identified by blood-based next generation sequencing (NGS) and response to the study medications (i.e., predictive biomarkers), progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to the study medications, evidence of activity of the study medications, and standard measures of clinical efficacy.
- For selected treatment arms requiring archival or new pretreatment tissue sample collection (all patients receiving trastuzumab/pertuzumab or atezolizumab): to perform retrospective central retesting for selected markers, to generate supplementary molecular profiling data, to potentially develop diagnostic assays, and/or to evaluate the association of tumor-specific biomarkers (i.e., markers of the tumor microenvironment) and response to therapy, including, but not limited to, whole genome sequencing, whole exome sequencing, RNA sequencing, fluorescence in situ hybridization, immunohistochemistry, and real-time polymerase chain reaction.
- For atezolizumab-treated patients: to determine and monitor C-reactive protein (CRP) and to evaluate the association of CRP with efficacy

Exploratory Pharmacokinetic and Immunogenicity Objectives

The exploratory pharmacokinetic/ immunogenicity objectives for this study are as follows:

- For atezolizumab-treated patients: to assess the immunogenicity of atezolizumab, potential relationships of the formation of such anti-drug antibodies (ADAs; anti-atezolizumab) with pharmacokinetics, safety, and efficacy.

Exploratory Patient-Reported Outcome Objectives

The exploratory patient-reported outcome (PRO) objectives are as follows:

- For atezolizumab-treated patients: to assess the impact of atezolizumab treatment on patient's functioning and health-related quality of life (HRQoL)
- For atezolizumab-treated patient: to assess overall treatment side effects burden

Study Design

Description of Study

This is a multicenter, non-randomized, open-label Phase IIa study conducted in the U.S. Six different treatment regimens will be evaluated simultaneously in groups of patients who have advanced solid tumors that has progressed following administration of standard of care treatment, or for whom no standard therapy exists, or for whom therapies that will convey clinical benefit are not available and/or are not suitable options per the treating physician's judgment, and in whom a trial of targeted therapy is considered the best available treatment option.

The study has closed screening and enrollment for patients with the following molecular alterations:

- EGFR-activating mutation – erlotinib
- BRAF-activating mutation – vemurafenib plus cobimetinib
- Hedgehog pathway potentially clinically relevant mutation (activating mutation of SMO or loss-of-function mutation of PTCH-1) – vismodegib
- HER2-activating mutation – trastuzumab plus pertuzumab
- HER2-overexpression or amplification - trastuzumab plus pertuzumab
- PD-L1 copy number gain, dMMR, MSI-H (without elevated tTMB), and alterations of DNA proofreading/repair genes (e.g., POLE, POLD1) – atezolizumab
- ALK genetic alterations (gene rearrangements, putative activating ALK mutations, ALK copy number gain) and selected alterations in ALK expression – alectinib
- Elevated tTMB – atezolizumab

For each of the study drugs, the dose and dosing schedule used in Study ML28897 is aligned with the currently approved dose and schedule in the product United States Package Insert (USPI) and Investigator's Brochure (IB). Trastuzumab, vemurafenib, erlotinib, vismodegib, alectinib, and atezolizumab have been studied and are approved for use as single agents. Erlotinib will be administered at 150 mg/day, the FDA-approved dose for use as a single agent, rather than 100 mg/day as used in combination with chemotherapy. Pertuzumab is approved for use in combination with trastuzumab and the combination of the two HER2-targeting monoclonal antibodies will be used in this study to target HER2-driven tumors. Although the approved indication for trastuzumab and pertuzumab is currently in combination with docetaxel, use of taxanes may not be appropriate in tumor types other than breast cancer and the objective of this study is to determine the efficacy and safety of the targeted agent(s). Cobimetinib is approved for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, and the combination regimen will be used in this study to target BRAF-driven tumors. Alectinib is approved for use in patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test.

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, *hepatocellular carcinoma, and melanoma*.

Atezolizumab will be used in this study for tumors with PD-L1 copy number gain, dMMR, MSI-H, elevated TMB, and/or alterations of DNA proofreading/repair genes (e.g., POLE, POLD1). Recommended safety monitoring will also be consistent with the approved labeled recommendations. Dose modifications will be managed per the Investigator's Brochure and USPI for each drug.

For trastuzumab, pertuzumab, erlotinib, vemurafenib, cobimetinib, alectinib, and atezolizumab, there are no differences between the drug formulations used in this study and the commercially approved drug product. For vismodegib, the 150-mg capsules are manufactured using the commercial formulation and by a process representative of commercially available product.

Patients will receive therapy for two cycles (8 weeks for oral drugs, 6 weeks for trastuzumab/pertuzumab and atezolizumab), and will then be evaluated for response. Patients with objective response or stable disease will continue therapy, with repeat evaluations to be performed according to the study flowchart specific for each study drug, until tumor progression, occurrence of unacceptable toxicity, or other discontinuation criteria are met.

As patients are enrolled and treated, the trial will be closely monitored; if patients with specific cancer subtypes are not benefiting from the targeted therapy, accrual of such patients will not be continued. Enrollment for specific subpopulations of patients in the atezolizumab arm will be capped.

For patients with mutations in more than one pathway who may be eligible for more than one study drug, the treating physician will determine the first pathway to target. Patients who have disease progression on one study treatment regimen and have another appropriate molecular alteration that is eligible for another targeted-pathway study treatment regimen may re-enroll in the study, provided they meet inclusion criteria for that study treatment regimen. A 21-day washout period is required between the last dose of the first treatment and the first dose of the next treatment.

Number of Patients

Approximately 765 patients will be enrolled in this study.

Target Population

Inclusion Criteria

Patients in all treatment arms except atezolizumab must meet the following criteria for study entry (note that all inclusion criteria for patients in the atezolizumab arm have been moved to Appendix 11 A11-4.1.1 and some may differ from related criteria in the list below):

- Able to understand the nature of this trial and provide written informed consent
- Age ≥ 18 years
- Willing and able to comply with study and follow-up procedures
- Life expectancy ≥ 12 weeks

- Histologically documented cancer with evidence of metastasis (solid tumors, not including hematologic malignancies). Patients with locally advanced, unresectable tumors may be eligible following approval of the medical monitor.
- Molecular testing results from CLIA-certified laboratories showing the following abnormality:

  ALK genetic alterations (gene rearrangements, putative activating non-synonymous ALK mutations, ALK copy number gain) and selected alterations in ALK expression
- Molecular testing results used for patient eligibility should be obtained from the most recent tumor biopsy. If molecular testing is not available from the most recent tumor biopsy, but all eligibility criteria are otherwise fulfilled, the patient can be enrolled based on the available molecular testing result. In these cases, a tissue sample from the most recent tumor biopsy must be provided for central re-testing, if available. Alternatively and for selected arms, molecular testing results used to determine patient eligibility could have been obtained from a recent blood sample (up to 2 months prior to enrollment) described in the study design.
- Patients who have received standard first-line therapy for metastatic cancer (except where no first-line therapy exists or, following approval by the medical monitor, in patients enrolling with locally advanced unresectable disease) in whom a trial of targeted therapy is considered the best available treatment option. Eligible patients should not have available approved therapies that would convey clinical benefit or such approved therapies are not considered suitable options per the treating physician's judgement
- No previous treatment with the specific assigned study drug or any other drug sharing the same target
- Measurable disease by RECIST v1.1
- ECOG PS score of 0 or 1
- Adequate hematologic function defined as the following:
  - Absolute neutrophil count (ANC) $\geq 1000/\mu L$
  - Hemoglobin (Hgb) ≥ 8 g/dL (may be achieved with erythropoietin agents or transfusions)
  - Platelets $\geq 75{,}000/\mu L$
- Adequate renal and liver function defined as the following:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ the upper limit of normal (ULN) ($\leq 5 \times$ ULN if considered due to primary or metastatic liver involvement)
  - Total bilirubin $\leq 1.5 \times$ ULN
  - Alkaline phosphatase $< 2 \times$ ULN ($< 5 \times$ ULN if considered due to tumor)
  - Serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 40 mL/min by Cockcroft-Gault formula

    Glomerular filtration rate estimation:

    {(140 – age) × (weight [in kg]) /

    (72 × serum creatinine [in mg/dL])} × 0.85 (if female)
- Male patients with prostate cancer who are receiving androgen blockade will be eligible for the study.
- Male patients must be willing to use acceptable methods of contraception. For additional inclusion criteria, please see the specific appendix for each study drug (Appendices 6–10).
- Female patients of childbearing potential must agree to use acceptable methods of contraception. For additional inclusion criteria, please see the specific appendix for each study drug.

Additional inclusion criteria specific to the study drug to be used are contained in the appropriate appendices.

Exclusion Criteria

Patients in all treatment arms except atezolizumab who meet any of the following criteria will be excluded from study entry (all exclusion criteria for patients in the atezolizumab arm have been moved to Appendix 11 A11-4.1.2):

- Patients with hematologic malignancies
- Concurrent administration of any other anti-cancer therapy (except male patients with prostate cancer who are receiving androgen blockade):
  - Bisphosphonates and denosumab are allowed.
  - Most recent anti-cancer therapy ≤ 28 days or who have not recovered from the side effects, excluding alopecia or mild residual neuropathy. Patients with alopecia or mild residual neuropathy may be eligible after discussion with the Medical Monitor
  - Radiation therapy within ≤ 14 days
- Active or untreated brain metastases
  - Patients with treated brain metastases are eligible if they have minimal neurologic symptoms, evidence of stable disease (for at least 1 month) or response on follow-up scan, and require no corticosteroid therapy.
- History of carcinomatous meningitis
- Uncontrolled concurrent malignancy (early stage is allowed if not requiring active therapy or intervention)
- Pregnant or breastfeeding, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Any of the following cardiovascular events within 6 months prior to study entry: myocardial infarction, malignant hypertension, severe/unstable angina, symptomatic congestive heart failure, cerebral vascular accident, or transient ischemic attack
- Pulmonary embolism within 30 days prior to study entry
- History or presence of clinically significant ventricular or atrial dysrhythmia > Grade 2
  - Patients with chronic, rate-controlled atrial arrhythmias who do not have other cardiac abnormalities are eligible.
- Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results
- Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol

All patients must meet the additional exclusion criteria for individual study drugs, as provided in the appendices as follows:

- Alectinib (Appendix 10)

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur after the last patient *completes treatment*.

In addition, the Sponsor may decide to terminate the study at any time.

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is the overall response rate (ORR) for those patients with measurable disease per RECIST v1.1. The ORR will be determined separately for each specific tumor type and molecular alteration.

The secondary efficacy outcome measures for this study are the following:

- Disease control rate (DCR)

- Progression-free survival (PFS)
- One-year survival rate (1-year overall survival [OS])
- Duration of response (DOR)

These endpoints will be determined separately for each specific tumor type and molecular alteration.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0) for patients enrolled prior to Version 6 of the protocol. The NCI CTCAE (v5.0) grading scale will be used for assessing adverse event severity for patients enrolled under Version 6 of the protocol and subsequent versions.
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Biomarker-related Outcome Measures

The biomarker-related outcome measures for this study may include but are not limited to:

- Genomic alterations (e.g. MSI, HER2) in tissue and blood to assess correlation with clinical outcome and change over time
- For atezolizumab-treated patients only: TMB in tissue and blood, CRP, and PD-L1 expression to assess correlation with clinical outcome and change over time

Pharmacokinetic and Immunogenicity Outcome Measures

The biomarker-related outcome measures for this study may include but are not limited to:

- For atezolizumab-treated patients enrolled under Version 6 of the protocol and later only: minimum observed serum atezolizumab concentration (C_{min}) prior to infusion will be evaluated within Cycle 1, 2, 3, 4, 8, 12, and 16. Atezolizumab serum concentrations are also evaluated at the end of treatment.
- For atezolizumab-treated patients enrolled under Version 6 of the protocol and later only: ADA incidence of formation in response to infusion with atezolizumab will be analyzed and potential relationships between ADA responses and the pharmacokinetics, efficacy, and safety of atezolizumab will be assessed when appropriate as data allow. ADA is evaluated at the same pre-treatment timepoints as PK is evaluated.

Patient-Reported Outcome Measures

The patient-reported outcome measures for this study are as follows:

- For atezolizumab-treated patients enrolled under Version 6 of the protocol and later only: Patient perspective regarding their day to day functioning, HRQoL, selected symptoms severity and impact of adverse events on their lives, will be measured by selected scales from the European Organization for the Research and Treatment of Cancer (EORTC) item library including Physical function, Role function, Emotional function, Pain, Fatigue, Cough, Dyspnea, Global Health Status or Bother with Adverse Events.

Investigational Medicinal Products

Study Treatment

Since there are slight differences in study design based upon the specific treatment received, please refer to the study design for each individual study treatment in the appendices as follows:

- Trastuzumab plus Pertuzumab (Appendix 6)
- Erlotinib (Appendix 7)
- Vemurafenib plus cobimetinib (Appendix 8)
- Vismodegib (Appendix 9)
- Alectinib (Appendix 10)

- Atezolizumab (Appendix 11)

Details of each study treatment, recommended concomitant medication, and prohibited medications are also contained in the appendices.

Statistical Methods

Final Efficacy Analyses

In this study, it is expected that approximately 20–75 patients will enroll in a disease and treatment cohort (i.e., specific tumor type treated with one of the study treatments), except for the atezolizumab treatment arm. *The final analysis will occur after all patients in a specific tumor and study treatment cohort have completed study assessments.* The ORR and disease control rate (DCR) will be estimated and the 70% and 95% confidence intervals will be constructed using exact binomial distribution.

It is anticipated that some (tumor-pathway) cohorts may reach less than 20–30 patients at the end of the study due to the rarity of the specific mutation in that disease. For these smaller (tumor-pathway) cohorts, ORR and DCR with confidence intervals will be calculated, although confidence intervals will be wider. Response rates (ORR and DCR) by study treatments will also be estimated across the various tumor types (where appropriate) along with 95% confidence intervals.

Median PFS and median DOR and their associated 95% confidence intervals, as well as 1-year OS, will be estimated using the Kaplan-Meier method. Descriptive analyses of safety and efficacy for each study arm (pathway summaries) will also be summarized across the various tumor types where appropriate.

Determination of Sample Size

The primary goal of this trial is to evaluate the efficacy of these targeted agents across a broad range of tumor types. Except for the atezolizumab arm, treatment of up to approximately 75 patients in a specific tumor type with an individual targeted therapy (tumor-pathway) cohort will allow estimation of the response rate to treatment. For rarer tumor/disease pathway combinations (e.g., HER2+ salivary, biliary, bladder etc.), enrollment may be limited to up to approximately 25 patients. With 25 patients, the margin of error (defined as one-half the width of the confidence interval) does not exceed 19.6% for a 95% confidence interval.

For the atezolizumab arm, up to approximately 70 patients with tTMB $\geq$ 10 and $<$ 16 mutations/Mb as determined by the FoundationOne or FoundationOne CDx test will be enrolled, with the expectation that up to approximately 50 patients will be IRC-evaluable. Once 50 IRC-evaluable patients with tTMB $\geq$ 10 and $<$ 16 mutations/Mb have been enrolled, given potential variations in mutations/Mb calling between FoundationOne / FoundationOne CDx and other assays, patients with ≥10 and <16 mutations/Mb from a non-FoundationOne / non-FoundationOne CDx assay will be allowed to continue to enroll, provided there is sufficient tissue available for a retrospective FoundationOne CDx test.

Furthermore, for the atezolizumab arm, up to approximately 200 patients with tTMB $\geq$ 16 mutations/Mb as determined by the FoundationOne or FoundationOne CDx test (local or by central re-testing) will be enrolled, with the expectation that up to approximately 150 will be IRC-evaluable.

With 180 patients, the margin of error does not exceed 7.5% for a 95% confidence interval.
With 150 patients, the margin of error does not exceed 8.0% for a 95% confidence interval.
With 75 patients, the margin of error does not exceed 11.3% for a 95% confidence interval.
With 50 patients, the margin of error does not exceed 13.9% for a 95% confidence interval.

Additionally, for the atezolizumab arm, enrollment will be restricted for specific subpopulations of patients with tTMB≥16 mutations/Mb who would be evaluable by IRC as follows:

- For the subpopulation with NSCLC, mUC, or melanoma, enrollment will be capped at up to approximately 30 patients (for all 3 tumor types combined, up to approximately 10 patients each).
- For the subpopulation with co-occuring tTMB ≥16 mutations/Mb and MSI-H, enrollment will be capped at up to approximately 20 patients (regardless of tumor type).

The total number of patients enrolled in each (tumor-pathway) cohort will vary depending on the feasibility of enrollment (mutation rates within tumor types) and interim analysis decisions. The specific tumor-pathway cohorts and their sample size are therefore difficult to anticipate in this study setting. It is expected that a total of approximately 765 patients will be enrolled in this study. Based on the results of interim analyses, as well as ongoing enrollment feasibility evaluations, the total target patient accrual to this study may be amended in collaboration with the Steering Committee.

Interim Analyses

In this trial, patients with a variety of tumor types will be enrolled on each drug or drug combination, since eligibility depends primarily on the existence of key mutations. It is anticipated that the efficacy of these targeted agents will vary depending on the tumor type and primary site. Therefore, for all treatment arms except atezolizumab, an interim analysis will be conducted when a cohort of 12 patients with a specific tumor type has been treated with one of the targeted therapies has a baseline and post-baseline scan, or has come off trial for an adverse event.

For the subpopulation with NSCLC, mUC, and melanoma, enrollment will be capped at approximately 10 patients (for all 3 tumor types combined, up to approximately 3 patients each).

These interim analyses will be utilized to identify (tumor-pathway) cohorts in which treatment is ineffective (i.e. futility analysis), either due to lack of efficacy or safety considerations, so that further accrual to such a cohort can be stopped.

For these interim analyses, ORR and DCR will be the efficacy endpoints considered. Any PFS or DOR data available will also be considered, although short follow-up may limit interpretation. Guidelines to assist in decision-making will be developed in collaboration with the study Steering Committee and will be tailored to the specific tumor types and the evolving treatment landscape. These guidelines will be provided in the study Steering Committee charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first line
2L	second line
ADA	anti-drug antibody, also called anti-therapeutic antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALK^{ATI}	ALK-alternative transcription initiation
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
AUC	area under the concentration–time curve
BID	twice daily
BML	below measurable limit
bTMB	blood tumor mutational burden
BUN	blood urea nitrogen
BWFI	bacteriostatic water for injection
CAD4	carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase
CBC	complete blood count
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CISH	chromogenic in situ hybridization
CK	creatine kinase
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration observed
C_{min}	minimum concentration observed
CMP	comprehensive metabolic profile
COSMIC	Catalogue of Somatic Mutations in Cancer
CPK	creatine phosphokinase
CR	complete response
CRC	colorectal cancer
CRF	Case Report Form

Abbreviation	Definition
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	cytotoxic T-lymphocyte-associated protein 4
ctDNA	circulating tumor DNA
cuSCC	cutaneous squamous cell carcinoma
DCR	disease control rate
DILI	drug-induced liver injury
dMMR	deficient mismatch repair
DOR	duration of response
EC	Ethics Committee
eCRF	electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-associated protein-like 4
EORTC	European Organization for the Research and Treatment of Cancer
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice

Abbreviation	Definition
GGT	gamma-glutamyl transferase
GHS	global health status
GI	Gastrointestinal
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HFSA	Heart Failure Society of America
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator Brochure
IC	immune cells
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	International Normalized Ratio
IRC	Independent Review Committee
IRB	Institutional Review Board
IRR	infusion-related reaction
IWRS	interactive web response system
KA	Keratoacanthoma
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
Mb	Megabase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK/ERK kinase
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability

Abbreviation	Definition
MSI-H	MSI-high
mUC	metastatic urothelial carcinoma
MUGA	multiple-gated acquisition (scan)
NCI	National Cancer Institute
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OCT	optical coherence tomography
ORR	overall response rate
OS	overall survival
1-year OS	one-year survival rate
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography (scan)
PF	physical function
PFS	progression-free survival
PK	pharmacokinetic
PO	per os, orally
POLD1	polymerase delta 1
POLE	polymerase epsilon
PR	partial response
PRO	patient-reported outcome
PTCH-1	protein patched homolog-1 (gene)
RECIST	Response Evaluation Criteria in Solid Tumors
RF	role functioning
RT-PCR	real-time polymerase chain reaction
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SCDI	Sarah Cannon Development Innovations
SCRI	Sarah Cannon Research Institute
SD	stable disease
SLS	sodium lauryl sulfate
SMO	smoothened (gene)

Abbreviation	Definition
STRN	Striatin
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TMB	tumor mutational burden
TSH	thyroid stimulating hormone
tTMB	tissue tumor mutational burden
ULN	upper limit of normal
USPI	U.S. Package Insert
VAF	variant allele frequency
WCBP	woman of childbearing potential
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 MOLECULAR ALTERATIONS AND TARGETED THERAPIES IN CANCER

During the last 25 years, markedly improved understanding of the molecular biology of neoplasia has highlighted the diversity of mechanisms capable of driving the cancer cell. Cancer types once viewed as being relatively homogeneous, such as colon cancer or adenocarcinoma of the lung, are now known to contain multiple subtypes defined by specific molecular genetic aberrations. This molecular sub-typing of cancer has enabled refinement of prognosis estimates and has also spurred the development of targeted therapies (imatinib, rituximab, trastuzumab, crizotinib, and vemurafenib) directed at critical targets defined on a molecular basis, rather than by cancer primary site or histology.

Currently, targeted agents are approved for use in specific cancer types (as defined by primary site), or a subset of that population harboring the specific molecular alteration. Usually, targeted agents have been approved in the cancer types that most frequently carry the specific molecular target. However, it is now clear that molecular alterations can be found in cancers from other primary sites, although often at low incidence levels. The potential therapeutic importance of these abnormalities is not clear, although anecdotal reports have documented activity with the investigational use of appropriate targeted therapy (Cappuzzo et al. 2006; Masago et al. 2009; LoRusso et al. 2011; Masago et al. 2011; Kelly et al. 2012; Minor et al. 2012). The relative rarity of these alterations (usually <5%) in any specific cancer type has made it difficult to identify sufficient patients for clinical trials.

Novel immune checkpoint inhibitors that use the body's adaptive immune system to selectively target cancer cells have been shown to demonstrate anti-tumor efficacy in a wide variety of tumors, including melanoma, bladder, and lung cancer. These agents act by blocking the type 1 T helper immune-repressive programmed cell death 1 (PD-1) pathway via antibodies to PD-1 or its ligands (e.g., programmed death-ligand 1 [PD-L1]). Various molecular abnormalities, such as PD-L1 expression levels (Gettinger et al. 2016), tumor mutational burden (Rizvi et al. 2015; Snyder et al. 2014; Johnson et al. 2016; Balar et al. 2017; Gandara et al. 2017; Kowanetz et al. 2017; Rosenberg et al. 2017) and deficiencies in mismatch repair enzymes (Mehnert et al. 2016; Le et al. 2015), have been associated with an enhanced anti-tumor response to immune checkpoint inhibitors.

With the recognition of the importance of molecular tumor abnormalities in identifying potentially effective treatment, numerous platforms have been developed to survey the cancer cell genome and detect critical molecular alterations. With increased molecular profiling, gene alterations for which a targeted agent exists, or which are associated with

improved efficacy of cancer immunotherapies, are being identified more frequently in tumor types for which these agents are currently not approved. These findings present a new opportunity to test the efficacy of currently available targeted agents and immunotherapies, based on the presence of the specific target rather than tumor primary site.

1.2 BACKGROUND ON THE THERAPEUTIC AGENTS

1.2.1 Trastuzumab (Herceptin®)/Pertuzumab (Perjeta®) (Treatment Arm Closed to Enrollment)

Human epidermal growth factor 2 (HER2)-targeted therapy has markedly improved the therapy of patients with HER2-positive breast cancer. The addition of trastuzumab, a HER2-targeted monoclonal antibody, to standard chemotherapy has substantially improved survival in the adjuvant and metastatic settings (Slamon et al. 2001; Slamon et al. 2011). Recently, the use of trastuzumab with pertuzumab, an antibody targeting a different portion of the HER2 receptor, has proven more effective than treatment with trastuzumab alone, suggesting a more complete blockade of the HER2 signaling pathway (Baselga et al. 2010; Baselga et al. 2012). Benefits of HER2-targeted therapy have also been demonstrated in HER2-overexpressing gastric and gastroesophageal adenocarcinomas (Van Cutsem et al. 2009).

At present, the diagnostic tests that most accurately predict responsiveness to HER2-targeted therapy are the measurement of HER2 overexpression/amplification by fluorescence in situ hybridization (FISH) (Lebeau et al. 2001) and strongly positive staining (3+) by immunohistochemistry (IHC). Recently, HER2 mutations have also been identified as more patients have comprehensive molecular profiling of their tumors. The significance of HER2 mutations is not clear, although there are anecdotal reports of responses to trastuzumab in patients with HER2-mutated non-small cell lung cancer (NSCLC) (Cappuzzo et al. 2006).

See the Trastuzumab Investigator's Brochure and Pertuzumab Investigator's Brochure for additional details.

1.2.2 Erlotinib (Tarceva®) (Treatment Arm Closed to Enrollment)

Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is currently approved for treatment of patients with advanced relapsed NSCLC or pancreatic cancer (also refer the Tarceva® U.S. Package Insert). Although erlotinib was originally tested and approved in an unselected NSCLC population, subsequent studies demonstrated marked activity in the subset of patients with an EGFR-activating mutation (Lynch et al. 2004). In these patients, first-line (1L) treatment with an EGFR-targeted agent is more effective than standard 1L chemotherapy (Maemondo et al. 2010). EGFR-activating mutations have been observed in a number of other cancer types; the significance of these mutations is unclear, although case reports have demonstrated response to EGFR inhibition (Masago et al. 2009; Masago et al. 2011).

In NSCLC, EGFR TKIs have shown high rates of response in patients with EGFR-activating mutations. Some association of erlotinib activity with gene copy number has been demonstrated in NSCLC, but this association as well as EGFR overexpression is relatively weak compared to the predictive power of EGFR-activating mutations (Hirsch et al. 2008; Forbes et al. 2010).

See the Erlotinib Investigator's Brochure for additional details.

1.2.3 Vemurafenib (Zelboraf®)/Cobimetinib (Cotellic®) (Treatment Arm Closed to Enrollment)

In melanoma, the V600E mutation is the most common mutation of the BRAF gene, and this mutation is highly correlated with activity of vemurafenib. Other less common BRAF mutations are of uncertain significance, although the activity of vemurafenib appears to be lower. BRAF V600E mutations have also been seen in a variety of other cancer types (Forbes et al. 2010; Pakneshan et al. 2013; Peters et al. 2013; Xing et al. 2013); the clinical significance of BRAF mutations in these other tumor types is also unclear.

Vemurafenib, a BRAF kinase inhibitor, has been approved for treatment of unresectable or metastatic melanomas harboring BRAF V600E mutations. In this subset of melanoma patients, vemurafenib produced a 48% response rate and a marked survival benefit when compared to standard treatment with dacarbazine (Chapman et al. 2011). In contrast, vemurafenib has no activity against melanomas that do not have BRAF mutations.

Cobimetinib in combination with vemurafenib has been approved in the U.S. for use in unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase MEK1 and MEK2. MEK proteins are upstream regulators of the extracellular signal-regulated kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E and V600K mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2. Cobimetinib and vemurafenib target two different kinases in the RAS/310 RAF/MEK/ERK pathway. Compared to either drug alone, co-administration of cobimetinib and vemurafenib resulted in increased apoptosis in vitro and reduced tumor growth in mouse implantation models of tumor cell lines harboring BRAF V600E mutations. Cobimetinib also prevented vemurafenib-mediated growth enhancement of a wild-type BRAF tumor cell line in an in vivo mouse implantation model. The GO28141 (coBRIM) study evaluated the addition of cobimetinib to vemurafenib in advanced BRAF V600-mutated melanoma patients and demonstrated an improvement in the time until the disease worsens (progression-free survival [PFS]) at 12.3 months versus 7.2 months (Larkin et al. 2015) and in overall survival (OS) at 22.3 months versus 17.4 months in the cobimetinib plus vemurafenib and vemurafenib plus placebo arms, respectively (Atkinson et al. 2015).

See the Vemurafenib Investigator's Brochure and Cobimetinib Investigator's Brochure for additional details.

1.2.4 Vismodegib (Erivedge®) (Treatment Arm Closed to Enrollment)

Vismodegib, a small molecule inhibitor of the hedgehog pathway, has been approved for treatment of adult patients with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery (Sekulic et al. 2012). In the pivotal Phase II trial, single agent treatment with vismodegib produced response rates of 30% and 43% in patients with metastatic and locally advanced basal cell carcinoma, respectively. Deregulation of the hedgehog signaling pathway has been identified in the vast majority of basal cell carcinomas, explaining the high level of activity of vismodegib in this malignancy. Mutations in smoothened (SMO) or protein patched homolog-1 (PTCH-1) lead to constitutive activation of the hedgehog pathway. These mutations, although rare, have been identified in multiple other tumor types, in which they are of undetermined therapeutic significance (Forbes et al. 2010; Wang et al. 2013).

See the Vismodegib Investigator's Brochure for additional details.

1.2.5 Alectinib (Alecensa®)

Alectinib is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by a Food and Drug Administration (FDA)-approved test. Alectinib was investigated in two randomized, multicenter Phase III open-label studies in patients with treatment-naive ALK-positive advanced NSCLC (Study BO28984, ClinicalTrials.gov number NCT02075840; Nokihara et al. 2016). Patients were randomized 1:1 to receive either alectinib or crizotinib. In these trials, alectinib demonstrated superior efficacy and lower toxicity in primary treatment of ALK-positive NSCLC compared to crizotinib (Hida et al. 2017; Peters et al. 2017). The most common ALK rearrangement in NSCLC, echinoderm microtubule-associated protein-like 4 (EML4-ALK), has also been reported in various other tumor types, including 2.4% reported in breast and colorectal cancers (Lin et al. 2009; Hallberg and Palmer 2013). Individual cases for successful treatment of patients with an striatin (STRN)-ALK or carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD)-ALK gene rearrangement using TKIs targeting ALK have been described in thyroid cancer or colorectal carcinoma, respectively (Pérot et al. 2014; Amatu et al. 2015). Additionally, alectinib has shown to be active on ALK activating point mutations like F1174L, R1275Q in cell line derived models (Sakamoto et al. 2011). Most putative ALK-activating mutations are suggested to reside in the kinase domain (Yau et al. 2015). Next to ALK gene rearrangements and mutations, also ALK copy number gain and amplification have been described to occur in various tumor types, are associated with poor outcome in CRC, and it was proposed that ALK high copy numbers predict sensitivity to ALK TKI in NSCLC (Salido et al. 2011; Khadija et al. 2012; Bavi et al. 2013; Zito Marino et al. 2016). Furthermore, an ALK variant (ALKATI) has been reported to result in overexpression of ALK protein in 11% of

melanoma patients and evidence of tumor shrinkage in response to ALK TKI suggests sensitivity of these tumors to ALK inhibitors (Wiesner et al. 2015). A Phase II trial (ClinicalTrials.gov number NCT02186821) evaluating ceritinib in non-NSCLC patients harboring ALK or ROS1 genetic alterations, or ALK overexpression, is currently ongoing.

See the Alectinib Investigator's Brochure for additional details.

1.2.6 Atezolizumab (Tecentriq®)

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as 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 is approved for the treatment of urothelial carcinoma, non-small cell lung cancer, small-cell lung cancer, *hepatocellular carcinoma, and melanoma*.

Urothelial Carcinoma

Atezolizumab is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, or for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 5\%$ of the tumor area) or are not eligible for any platinum-containing chemotherapy regardless of level of tumor PD-L1 expression. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Lung Cancer

Atezolizumab is approved in the United States for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with NSCLC who have EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab. Atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin, is also approved for the 1L treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. Atezolizumab is also approved for the 1L treatment of adult patients with extensive-stage small cell lung cancer in combination with carboplatin and etoposide.

Hepatocellular carcinoma

Atezolizumab, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.

Melanoma

Atezolizumab, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

1.2.7 Atezolizumab in Patients with Elevated Tumor Mutational Burden

A growing body of evidence points to higher tumor mutational burden being correlated with better clinical outcomes with checkpoint inhibitor therapies. The higher mutational burden in these tumors likely produces an array of immunogenic neoantigens that renders greater sensitivity to the effects of the immune system (Schumacher and Schreiber 2015). A study in NSCLC showed that higher nonsynonymous mutational burden was associated with improved efficacy to PD-1–PD-L1 interaction blockade in two independent cohorts (Rizvi et al. 2015). Furthermore, it has also been shown that elevated tissue TMB (tTMB) is associated with improved atezolizumab efficacy in patients with NSCLC in 1L or second line (2L)+ (Kowanetz et al. 2017). Notably, a recent retrospective study with 987 biomarker evaluable patients showed elevated tTMB (≥16 mutations/megabase [Mb]) is associated with improved ORR and DOR among patients with NSCLC, metastatic urothelial carcinoma (mUC) and melanoma (Legrand et al. 2018). This effect was shown to be independent of the number of lines of therapy.

Atezolizumab has also shown improved efficacy in 1L and 2L+ NSCLC patients with elevated blood TMB (bTMB) (Gandara et al. 2017; Velcheti et al. 2018). In 1L NSCLC patients, interim data showed that median PFS for atezolizumab-treated patients was 9.5 vs 2.8 months for bTMB high (≥ 16 mutations) vs low (< 16 mutations); hazard ratio (HR), 0.49 (90% confidence interval [CI], 0.23, 1.04; P = 0.11). Furthermore, PFS HRs improved as bTMB scores increased, further demonstrating the biological clinical relevance of bTMB as a predictive biomarker (Velcheti et al. 2018).

Additionally, a higher mutational burden has been shown to correlate with a higher rate of response in melanoma patients treated with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) therapies (Snyder et al. 2014). And elevated mutational burden has been shown to be associated with improved atezolizumab efficacy in 1L cisplatin-ineligible metastatic urothelial carcinoma patients and in metastatic urothelial carcinoma patients who had progressed on cisplatin-based chemotherapies (Balar et al. 2017; Rosenberg et al. 2017).

Research has also shown that mismatch repair status (as determined by microsatellite instability levels) could be a predictor of efficacy of immune checkpoint blockade, as

evidenced by greater efficacy of anti–PD-1 blockade in colorectal cancers with mismatch repair deficiency compared to tumors that are mismatch repair proficient (Le et al. 2015). Furthermore, presence of mutations in genes of the DNA proofreading/repair system, such as DNA polymerase epsilon (POLE) or polymerase delta 1 (POLD1) are associated with an elevated tumor mutational burden and increased expression of PD-L1, but mostly associated with a microsatellite stable phenotype in uterine and colon cancer (Howitt et al. 2015; Cancer Genome Atlas Network 2012). Based on a case report of an endometrial cancer patient responding to a PD-1 inhibitor, it was suggested that presence of POLE mutations may identify a subset of cancer that may be responsive to immune checkpoint blockade (Mehnert et al. 2016). PD-L1 amplification has been shown to correlate with higher PD-L1 expression both by mRNA and at protein levels (Straub et al. 2016). Direct correlation between PD-L1 amplification and mutational burden has also been reported (Budczies et al. 2016). A case report described a patient with metastatic cancer of unknown primary origin harboring multiple mutations and PD-L1 amplifications. This patient experienced partial remission after being treated with a checkpoint inhibitor (Gröschel et al. 2016). Taken together, these findings indicate that patients with PD-L1 copy number gain may benefit from anti-PD-L1 treatment (Inoue et al. 2016).

See the Atezolizumab Investigator's Brochure for additional details.

1.3 RATIONALE FOR CONDUCTING THIS STUDY

This open-label Phase IIa trial will evaluate the efficacy and safety of several agents in tumor types other than their current United States (U.S.) FDA-approved indications. The study will focus on the following molecular pathways and abnormalities: HER2; EGFR; BRAF; the hedgehog pathway; ALK; and PD-L1 copy number gain, deficient mismatch repair (dMMR), microsatellite instability-high (MSI-H), elevated tumor mutational burden (TMB), and/or alterations of DNA proofreading/repair genes (e.g., POLE, POLD1). Molecular alterations of each of these targets have been recognized in multiple tumor types in addition to the ones for which the drugs are currently indicated. Although mutations in some tumor types are based on small sample size, Table 1 provides estimates regarding the frequency of these alterations in various tumor types. The eight drugs to be included in this trial target the molecular abnormalities described above, and are as follows: trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib, vismodegib, alectinib, and atezolizumab. Treatment arms for trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib and vismodegib have been closed to further enrollment. In the future, this protocol may be amended to include additional drugs after market approval in specific cancer types.

Table 1 Estimated Incidence of Specific Mutations in Various Cancer Types (from COSMIC Database)

Tumor – Primary Tissue	% Mutated	Tumor – Primary Tissue	% Mutated
EGFR[a]		BRAF[a]	
Peritoneum	18%	Thyroid	41%
Prostate	7%	Eye	12%
CNS	6%	Genital tract	12%
Stomach	6%	Large intestine	12%
Ovary	5%	Ovary	12%
Adrenal gland	4%	Small intestine	8%
Biliary tract	4%	Biliary tract	6%
Salivary gland	4%	Meninges	5%
Thyroid	4%	CNS	4%
Eye	3%	Endometrium	4%
Upper aerodigestive tract	3%	Hematopoietic and lymphoid tissue	4%
Esophagus	2%	Prostate	4%
Urinary tract	2%	Gastrointestinal tract	3%
Breast	1%	Adrenal gland	2%
Hematopoietic and lymphoid tissue	1%	Lung	2%
Kidney	1%	Esophagus	2%
Large intestine	1%	Pancreas	2%
Skin	1%	Soft tissue	2%
Soft tissue	1%		
Thymus	1%		
Hedgehog Pathway[a]		HER2[a]	
Upper aerodigestive tract	52%	Ovary	3%
Liver	8%	CNS	2%
Ovary	8%	Liver	2%
Large intestine	7%	Lung	2%
Esophagus	7%	Upper aerodigestive tract	2%
CNS	7%	Large intestine	1%
Breast	3%	Pancreas	1%
Lung	1%		

Table 1 Estimated Incidence of Specific Mutations in Various Cancer Types (from COSMIC Database (cont.)

Tumor – Primary Tissue	% Mutated	Tumor – Primary Tissue	% Mutated
ALK			
ALK Rearrangements [a,b]		ALK Mutations in and Around Kinase Domain (amino acid 1062-1311) [a,c]	
Soft tissue	39%	Bladder	2%
Hematopoietic and lymphoid tissue	26%	Melanoma	1.9%
Skin	13%	Esophagus	1.4%
Lung	6%	Lung	1%
CRC	2%	Uterine	1%
Breast	2%	Breast	0.6%
Thyroid	2%	Large intestine	0.5%
		Head and neck	0.4%
		Stomach	0.25%
ALK Copy Number Gain [a,c,d]			
Ovarian	4.1%		
CRC	3.4%		
Uterine	2.6%		
Bladder	1.7%		
Lung squamous	1.6%		
Cervical	1.4%		
Breast	1.1%		
Liver	1.1%		
Renal	1.1%		

Table 1 Estimated Incidence of Specific Mutations in Various Cancer Types (from COSMIC Database) (cont.)

Tumor – Primary Tissue	% Mutated	Tumor – Primary Tissue	% Mutated
Other			
PD-L1 Copy Number Gain [a,c]		dMMR/MSI-H [a,e]	
Sarcoma	4.7%	Thyroid	63%
Ovarian	4.3%	Stomach	22%
Head and neck	3.7%	Endometrial	22%
Cervical	2.7%	HCC	16%
Stomach	2.5%	CRC	13%
Bladder	2.5%	Melanoma	11%
Lung squamous	2.4%	Ampullary carcinoma	10%
Esophagus	2.2%	Ovarian	10%
Breast	2.0%	Cervical	8%
Uterine	1.7%	Esophagus	7%
Melanoma	1.4%	HNSCC	3%
CRC	1.3%	RCC	2%
NSCLC	1.2%	Ewing sarcoma	2%
Pancreas	1.2%	Other tumor types	0–2%
Liver	0.8%		
Lung adeno	0.8%		
Prostate	0.5%		
ccRCC	0.4%		
GBM	0.2%		
Elevated TMB [a,f]		**POLE/POLD1** [a,i]	
Endometrium	17.4%	Endometrium	9%
Urothelial carcinoma	10.0%	CRC	3%
Prostate	4.9%		
Gall bladder	1.2%		

ALK = anaplastic lymphoma kinase; ccRCC = clear cell renal cell carcinoma; CRC = colorectal cancer; dMMR = deficient mismatch repair; GBM = glioblastoma multiforme; HCC = hepatocellular carcinoma; HNSCC = head and neck squamous cell carcinoma; MSI-H = microsatellite instability-high; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; POLE = polymerase epsilon; POLD1 = polymerase delta 1; RCC = renal cell carcinoma.

[a] From Forbes et al. 2010.

[b] From Lin et al. 2009.

[c] From Gao et al. 2013; Cerami et al. 2012.

[d] From Bavi et al. 2013.

[e] From Dudley et al. 2016.

[f] From Pal et al. 2016; Frampton et al. 2016; Chalmers et al. 2017.

[i] From Lee et al. 2016

1.4 RISK/BENEFIT ASSESSMENT

The majority of cancers are associated with molecular alterations that dysregulate key oncogenic pathways influencing cell growth and survival. Knowledge of specific pathway alterations has informed rational clinical use of targeted agents. When a driver genetic alteration (i.e., mutation that dysregulates a protein on which the cancer cell depends) is intercepted by a targeted small molecule or monoclonal antibody, significant clinical responses may result. The activity of therapies including trastuzumab, pertuzumab, vemurafenib, cobimetinib, erlotinib, vismodegib, alectinib, and atezolizumab has resulted in improved clinical outcomes for patients with tumors that contain identified molecular pathway alterations. Use of these agents has been studied and approved in tumor types harboring the highest incidence of these molecular abnormalities. However, these potentially actionable molecular pathway alterations may exist in other tumor types, but the low incidence of these identified in other tumor types has made study difficult due to small patient populations and the need to screen large numbers of patients. Nevertheless, there is scientific rationale to support use of targeted agents in treating cancers for which an actionable target has been identified. Use of cancer molecular profiling may offer a means to improve the care of patients with cancers other than the previously studied and approved indications.

Patients considered for enrollment in this study will be those with advanced solid tumors whose cancer has progressed following administration of standard of care treatment, or for whom no standard therapy exists, or for whom therapies that will convey clinical benefit are not available and/or are not suitable options per the treating physician's judgment, and in whom a trial of targeted therapy is considered the best available treatment option. Patients with rare tumor types will be included.

The safety plan for this study is designed to ensure patient safety by utilizing inclusion and exclusion criteria that is consistent with the known safety profiles of the investigational agents. A Steering Committee composed of multidisciplinary members of Genentech, Sarah Cannon, and external experts will be set up to review safety data at periodic intervals in order to identify the emergence of new or increased safety signals. Considering that the toxicity profile of these approved agents has been well characterized together with rigorous monitoring of the known toxicities of the individual agents, the proposed study poses an acceptable risk in these patient populations.

1.4.1 *COVID-19 Benefit Risk Assessment*

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear whether or how cancer therapies such as chemotherapy or targeted therapy impact the incidence or severity of COVID-19. It is

not known whether any of the agents being investigated in this study will increase the risk of infection with SARS-CoV-2.

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021; see additional information for patients receiving atezolizumab in Section 1.4.2).

No interactions are expected with the available COVID-19 vaccinations and any of the molecules that are actively being administered in this study (trastuzumab/pertuzumab and atezolizumab - see additional information regarding patients receiving atezolizumab in Section 1.4.2).

Society for Immunotherapy of Cancer [SITC] and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label.

Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4).

1.4.2 COVID-19 Benefit-Risk Assessment for Patients Receiving Atezolizumab

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

Severe SARS-CoV-2 infection appears to be associated with a cytokine- release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-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 SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic

features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

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

Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is to evaluate the efficacy of trastuzumab plus pertuzumab, erlotinib, vemurafenib plus cobimetinib, vismodegib, alectinib, and atezolizumab in patients with advanced solid tumors and: 1) with molecular alterations (mutations, gene expression abnormalities, elevated TMB) predictive of response to one of these agents, 2) with no prior approved indication for use of these agents, and 3) for whom therapies that will convey clinical benefit are not available and/or are not suitable options per the treating physician's judgment.

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To evaluate the safety and tolerability of the study medications for the tumor types studied
- To collect and store molecular profiling data of all patients treated in this study, for the purpose of correlating treatment response with patterns of tumor genetic abnormalities

2.3 EXPLORATORY BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- All disease cohorts: to evaluate the association of the levels and nature of somatic tumor-specific mutations identified by blood-based next generation sequencing (NGS) and response to the study medications (i.e., predictive biomarkers), progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to the study medications, evidence of activity of the study medications, and standard measures of clinical efficacy.
- For selected treatment arms requiring archival or new pretreatment tissue sample collection (all patients receiving trastuzumab/pertuzumab or atezolizumab): to perform retrospective central retesting for selected markers, to generate supplementary molecular profiling data, to potentially develop diagnostic assays, and/or to evaluate the association of tumor-specific biomarkers (i.e., markers of the tumor microenvironment) and response to therapy, including, but not limited to, WGS, WES, RNA sequencing, FISH, IHC, and RT-PCR.
- For atezolizumab-treated patients: to determine and monitor C-reactive protein (CRP) and to evaluate the association of CRP with efficacy

2.4 EXPLORATORY PHARMACOKINETIC AND IMMUNOGENICITY OBJECTIVES

The exploratory pharmacokinetic/ immunogenicity objectives for this study are as follows:

- For atezolizumab-treated patients: to assess the immunogenicity of atezolizumab, potential relationships of the formation of such anti-drug antibodies (ADAs; anti-atezolizumab) with pharmacokinetics, safety, and efficacy.

2.5 EXPLORATORY PATIENT-REPORTED OUTCOME OBJECTIVES

The exploratory patient-reported outcome (PRO) objectives are as follows:

- For atezolizumab-treated patients: to assess the impact of atezolizumab treatment on patient's functioning and health-related quality of life (HRQoL)
- For atezolizumab-treated patient: to assess overall treatment side effects burden

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a multicenter, non-randomized, open-label Phase IIa study conducted in the U.S. Six different treatment regimens will be evaluated simultaneously in groups of patients who have advanced solid tumors that has progressed following administration of standard of care treatment, or for whom no standard therapy exists, or for whom therapies that will convey clinical benefit are not available and/or are not suitable options

per the treating physician's judgment, and in whom a trial of targeted therapy is considered the best available treatment option.

The study has closed screening and enrollment for patients with the following molecular alterations:

- EGFR-activating mutation –erlotinib
- BRAF-activating mutation –vemurafenib plus cobimetinib
- Hedgehog pathway potentially clinically relevant mutation (activating mutation of SMO or loss-of-function mutation of PTCH-1) –vismodegib
- HER2-activating mutation –trastuzumab plus pertuzumab
- HER2-overexpression or amplification - trastuzumab plus pertuzumab
- PD-L1 copy number gain, dMMR, MSI-H (without elevated tTMB), and alterations of DNA proofreading/repair genes (e.g., POLE, POLD1) –atezolizumab
- ALK genetic alterations (gene rearrangements, putative activating ALK mutations, ALK copy number gain) and selected alterations in ALK expression – alectinib
- Elevated tTMB – atezolizumab

For each of the study drugs, the dose and dosing schedule used in Study ML28897 is aligned with the currently approved dose and schedule in the product United States Package Insert (USPI) and Investigator's Brochure (IB) (see Section 4.3). Trastuzumab, vemurafenib, erlotinib, vismodegib, alectinib, and atezolizumab have been studied and are approved for use as single agents. Erlotinib will be administered at 150 mg/day, the FDA-approved dose for use as a single agent, rather than 100 mg/day as used in combination with chemotherapy. Pertuzumab is approved for use in combination with trastuzumab and the combination of the two HER2-targeting monoclonal antibodies will be used in this study to target HER2-driven tumors. Although the approved indication for trastuzumab and pertuzumab is currently in combination with docetaxel, use of taxanes may not be appropriate in tumor types other than breast cancer and the objective of this study is to determine the efficacy and safety of the targeted agent(s). Cobimetinib is approved for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, and the combination regimen will be used in this study to target BRAF-driven tumors. Alectinib is approved for use in patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test.

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, *hepatocellular carcinoma, and melanoma* (see Section 1.2.6 for current approval).

Atezolizumab will be used in this study for tumors with PD-L1 copy number gain, dMMR, MSI-H, elevated TMB, and/or alterations of DNA proofreading/repair genes (e.g., POLE, POLD1). Recommended safety monitoring will also be consistent with the approved

labeled recommendations. Dose modifications will be managed per the Investigator's Brochure and USPI for each drug.

For trastuzumab, pertuzumab, erlotinib, vemurafenib, cobimetinib, alectinib, and atezolizumab, there are no differences between the drug formulations used in this study and the commercially approved drug product. For vismodegib, the 150-mg capsules are manufactured using the commercial formulation and by a process representative of commercially available product.

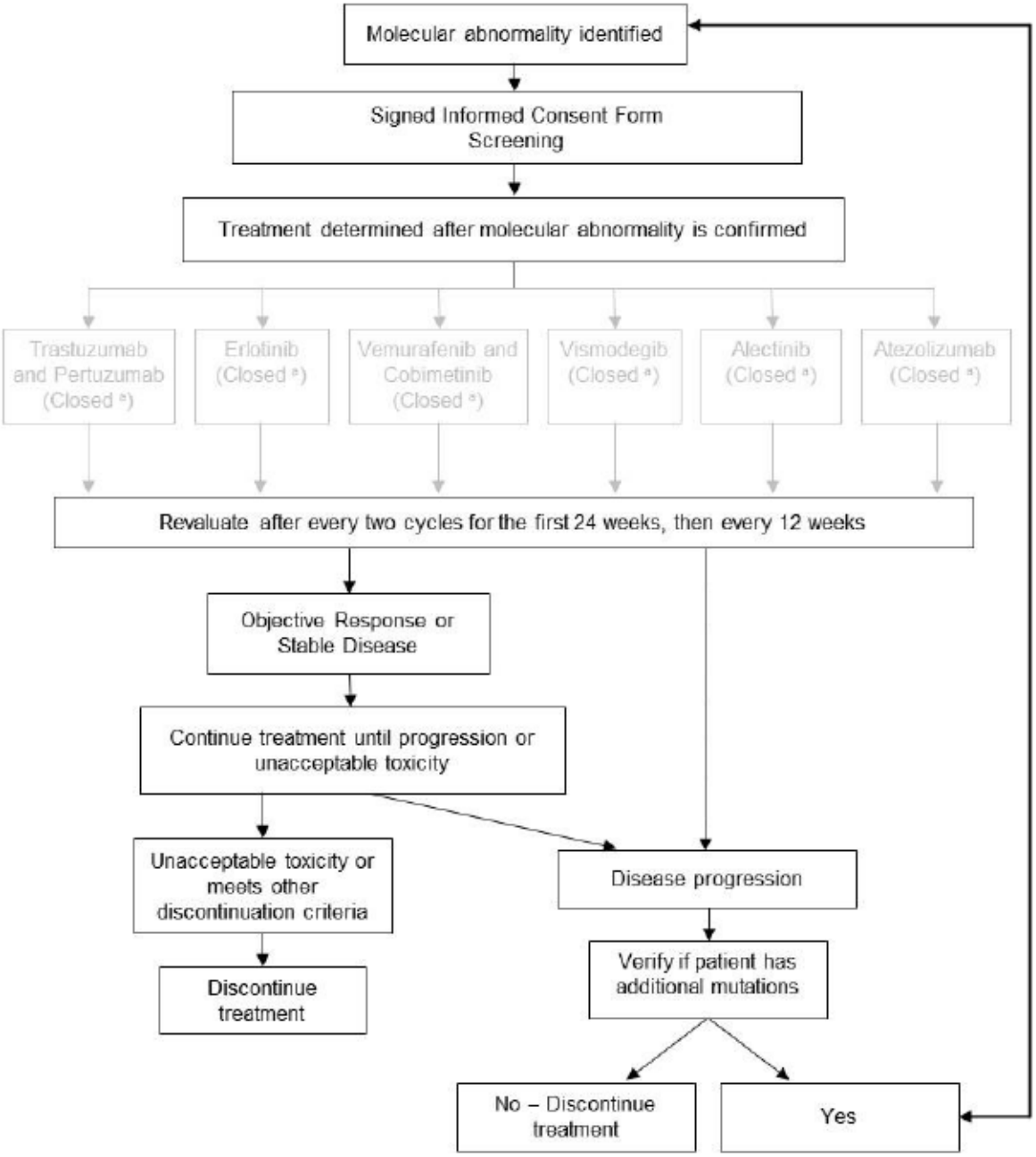
Patients will receive therapy for two cycles (8 weeks for oral drugs, 6 weeks for trastuzumab/pertuzumab and atezolizumab), and will then be evaluated for response. Patients with objective response or stable disease will continue therapy, with repeat evaluations to be performed according to the study flowchart specific for each study drug (Appendix 6–11), until tumor progression, occurrence of unacceptable toxicity, or other discontinuation criteria are met (see Section 4.6).

As patients are enrolled and treated, the trial will be closely monitored; if patients with specific cancer subtypes are not benefiting from the targeted therapy, accrual of such patients will not be continued (see Section 6.8). Enrollment for specific subpopulations of patients in the atezolizumab arm will be capped. For details, see Sections 6.1 and 6.8.

The study schema is shown in Figure 1 (regimen-specific schemas are included in Appendix 6–11).

For patients with mutations in more than one pathway who may be eligible for more than one study drug, the treating physician will determine the first pathway to target. Patients who have disease progression on one study treatment regimen and have another appropriate molecular alteration that is eligible for another targeted-pathway study treatment regimen may re-enroll in the study, provided they meet inclusion criteria for that study treatment regimen. A 21-day washout period is required between the last dose of the first treatment and the first dose of the next treatment.

Figure 1 Main Study Schema



[a] Treatment arm closed to screening and enrollment.

The schedule of assessments for each treatment are provided in Appendix 6–11.

Steering Committee

A Steering Committee will be formed of multidisciplinary members from Genentech, Sarah Cannon Research Institute (SCRI), and external experts to provide clinical and methodological expertise to the oversight of the study. Clinically, the Steering Committee expertise will be used to review data and provide consultation in evaluating

efficacy and safety data for each (tumor-pathway) cohort, as well as for each study arm (pathways across tumor types, where appropriate). From a methods perspective, the Steering Committee will make recommendations regarding the eligibility of patients with rare/uncharacterized molecular alterations, emerging molecular testing techniques, statistical analyses, and clinical trial design. The Steering Committee will operate according to a pre-specified charter.

The primary responsibility of the Steering Committee is to review the available safety and efficacy data and to make recommendations on continued treatment of patients in the study. For the atezolizumab arm, the Steering Committee will review the safety data only. Safety will be reviewed by the Steering Committee to identify the emergence of new or increased safety signals. The Steering Committee will also review efficacy data and advise on a cohort's continued accrual of patients with specific tumor types to targeted therapy at interim analyses (see Section 6.8). The Steering Committee will provide review of emerging data regarding diagnostic testing methodologies and platforms, as well as molecular alterations. Genentech will consider the Steering Committee's recommendations in any decisions regarding study conduct.

Members in the Steering Committee will include, but are not be limited to: a) Genentech medical team representative, b) Genentech study biostatistician, c) study investigators from SCRI, and d) medical oncology disease area specialists external to SCRI and Roche/Genentech. The external medical specialists will include experts in oncologic diseases expected to be seen in the study as well as expert(s) in molecular pathology.

The Steering Committee will meet approximately two to three times a year to review safety and efficacy data for all patients except those receiving atezolizumab. For the atezolizumab arm, the Steering Committee will review the safety data only. For all treatment arms except atezolizumab, an interim analysis for each (tumor-pathway) cohort will be conducted when 12 patients have evaluable response data. The Steering Committee will convene to review these data and to identify (tumor-pathway) cohorts in which treatment is ineffective (i.e. futility analysis), either due to lack of efficacy or safety considerations, so that further accrual to such a cohort can be stopped. The Steering Committee may convene on an ad hoc basis in the event that a safety signal is identified.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur after the last patient *completes treatment*.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale For Patient Population

Molecular profiling of various cancers is being conducted with increasing frequency. Some academic centers have established genetic clinics and some cancer centers routinely collect and archive patient tumor samples for further molecular investigation. Such tests may identify a spectrum of actionable genomic alterations within an individual tumor (including mutations, chromosomal rearrangements, copy number changes, or epigenetic alterations), which may ultimately facilitate an individualized approach for some patients with cancer. Biomarker assays used to select patients for this study are reliable, validated, and/or have been approved within specific tumor types. Patients having tumors with identified variants of uncertain significance will not be included in this study. Patients with mutations that are not well characterized may be considered for inclusion after consultation by the Medical Monitor with the Sponsor and/or the Steering Committee scientific experts. Agreement will be a consensus based on review of existing clinical and nonclinical data. Therapeutic agents for which the mechanism of action is generally known and for which appropriate predictive biomarkers exist have been chosen for study. This study is designed to decipher the effects of a targeted agent against a specific molecular aberration while agnostic of the histologic tumor. Sometimes referred to as a basket trial, this study aims to provide insight into the functionality of the same genomic aberration across different tumor types.

Patients with tumors that have been tested by a molecular pathologist at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory and found to contain a potentially targetable molecular alteration for which there exists an approved Genentech therapy may be enrolled in this study. Molecular characterization should have been performed on the most recently available tumor sample or on a recent blood sample prior to enrollment in this study for selected treatment arms (see Appendix 5 for details). A copy of the pathology/molecular testing report must be available for review by the medical monitors and it is recommended that tumor samples be collected and stored for further characterization.

Collection of tumor specimens in the context of this clinical study is a high priority and will enable the assessment of study objectives, development of diagnostic assays, and enable future research. Submission of tissue samples is mandatory for patients without valid TMB score reported by FoundationOne or FoundationOne CDx (Foundation Medicine, Inc.) and receiving atezolizumab to enable assessment of study endpoints and assay development (A11-4.5.1.2.1).

3.3.2 Rationale For Biomarker Assessments

Advanced solid tumors constitute a heterogeneous disease, and mutations and gene abnormalities have been shown to vary among patients and evolve over time. For patients receiving trastuzumab/pertuzumab or atezolizumab, tumor tissue samples are required to enable assessment of study objectives and allow assay development (see

Appendix 6 [trastuzumab plus pertuzumab] and Appendix 11 [atezolizumab]. Furthermore, all patients are encouraged to submit optional tissue samples collected pre-treatment, on study (for atezolizumab arm only), and/or at disease progression to help assess the evolution of genomic alterations and changes in the tumor microenvironment. The scientific understanding of tumor biology is constantly evolving and technological standards/assay standards are changing rapidly. Tissue samples will be used to generate supplementary molecular profiling or biomarker data that help to better understand disease biology and evaluate the association of tumor-specific biomarkers, including the tumor microenvironment and response to therapy. Samples may also be used to support future assay development. Methodologies used may include, but are not limited to WGS, WES, FISH, IHC, RNA sequencing, and/or RT-PCR.

Blood samples will be collected to examine the level and nature of tumor-specific molecular alterations associated with the relevant study medication. It is also of interest to assess the presence or absence of resistance mutations in blood over time throughout treatment. The mutations evaluated will include those mutations that are specifically relevant to the study drug, including bTMB, and may also include tumor-specific mutations that are of currently unknown significance.

Blood samples will be collected pre-dose at baseline (C1D1), at Day 1 of Cycle 3 (C3D1), and at the time of disease progression for circulating tumor DNA (ctDNA) extraction to enable analysis to identify somatic mutations, including bTMB, that may be predictive of response to study drug, may be associated with progression to a more severe disease state, may be associated with acquired resistance to the study medications, or that may increase the knowledge and understanding of disease biology. Samples may also be used to support assay development and regulatory filings. Methodologies used may include, but are not limited to NGS.

For patients receiving atezolizumab, additional blood samples will be collected to explore potential relationships between biomarkers in blood and tumor tissue with efficacy, safety, pharmacokinetics, immunogenicity; other biomarker endpoints will be explored as appropriate on the basis of available data.

3.3.3 Rationale For Patient-Reported Outcome Assessments (Atezolizumab Arm Only)

Patients' perspective regarding their conditions and treatment impact on symptoms, functioning, and quality of life will be documented through completion of fit for purpose scales from the EORTC library.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure for this study is the overall response rate (ORR) for those patients with measurable disease per RECIST v1.1; see Appendix 4. The ORR will be determined separately for each specific tumor type and molecular alteration.

The secondary efficacy outcome measures for this study are the following:

- DCR
- PFS
- One-year survival rate (1-year OS)
- DOR

These endpoints will be determined separately for each specific tumor type and molecular alteration.

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0) for patients enrolled prior to Version 6 of the protocol. The NCI CTCAE (v5.0) grading scale will be used for assessing adverse event severity for patients enrolled under Version 6 of the protocol and subsequent versions.
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

3.4.3 Biomarker-Related Outcome Measures

The biomarker-related outcome measures for this study may include but are not limited to:

- Genomic alterations (e.g. MSI, HER2) in tissue and blood to assess correlation with clinical outcome and change over time
- For atezolizumab-treated patients only: TMB in tissue and blood, CRP, and PD-L1 expression to assess correlation with clinical outcome and change over time

3.4.4 Pharmacokinetic and Immunogenicity Outcome Measures

The following pharmacokinetic (PK) and immunogenicity parameters will be evaluated from the serum concentration-time profiles of atezolizumab, when appropriate as data allow:

- For atezolizumab-treated patients enrolled under Version 6 of the protocol and later only: minimum observed serum atezolizumab concentration (C_{min}) prior to infusion will be evaluated within Cycles 1, 2, 3, 4, 8, 12, and 16. Atezolizumab serum concentrations are also evaluated at the end of treatment.

- For atezolizumab-treated patients enrolled under Version 6 of the protocol and later only: ADA incidence of formation in response to infusion with atezolizumab will be analyzed and potential relationships between ADA responses and the pharmacokinetics, efficacy, and safety of atezolizumab will be assessed when appropriate as data allow. ADA is evaluated at the same pre-treatment timepoints as PK is evaluated.

3.4.5 Patient-Reported Outcome Measures

The patient-reported outcome measures for this study are as follows:

- For atezolizumab-treated patients enrolled under Version 6 of the protocol and later only: Patient perspective regarding their day to day functioning, HRQoL, selected symptoms severity and impact of adverse events on their lives, will be measured by selected scales from the European Organization for the Research and Treatment of Cancer (EORTC) item library including Physical function, Role function, Emotional function, Pain, Fatigue, Cough, Dyspnea, Global Health Status or Bother with Adverse Events.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients in all treatment arms except atezolizumab must meet the following criteria for study entry (note that all inclusion criteria for patients in the atezolizumab arm have been moved to A11-4.1.1 and some may differ from related criteria in the list below):

- Able to understand the nature of this trial and provide written informed consent
- Age ≥ 18 years
- Willing and able to comply with study and follow-up procedures
- Life expectancy ≥ 12 weeks
- Histologically documented cancer with evidence of metastasis (solid tumors, not including hematologic malignancies). Patients with locally advanced, unresectable tumors may be eligible following approval of the medical monitor.
- Molecular testing results from CLIA-certified laboratories showing the following abnormality:
  - ALK genetic alterations (gene rearrangements, putative activating non-synonymous ALK mutations, ALK copy number gain) and selected alterations in ALK expression (see Appendix 5 and Appendix 10 for specific requirements)

- Molecular testing results used for patient eligibility should be obtained from the most recent tumor biopsy. If molecular testing is not available from the most recent tumor biopsy, but all eligibility criteria are otherwise fulfilled, the patient can be enrolled based on the available molecular testing result. In these cases, a tissue sample from the most recent tumor biopsy must be provided for central re-testing, if available. Alternatively and for selected arms, molecular testing results used to determine patient eligibility could have been obtained from a recent blood sample (up to 2 months prior to enrollment) (see Appendix 5 for specific requirements) described in the study design.
- Patients who have received standard first-line therapy for metastatic cancer (except where no first-line therapy exists or, following approval by the medical monitor, in patients enrolling with locally advanced unresectable disease) in whom a trial of targeted therapy is considered the best available treatment option. Eligible patients should not have available approved therapies that would convey clinical benefit or such approved therapies are not considered suitable options per the treating physician's judgement
- No previous treatment with the specific assigned study drug or any other drug sharing the same target
- Measurable disease by RECIST v1.1 (see Appendix 4)
- ECOG PS score of 0 or 1 (see Appendix 1)
- Adequate hematologic function defined as the following:
  - Absolute neutrophil count (ANC) $\geq 1000/\mu L$
  - Hemoglobin (Hgb) ≥ 8 g/dL (may be achieved with erythropoietin agents or transfusions)
  - Platelets $\geq 75{,}000/\mu L$
- Adequate renal and liver function defined as the following:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ the upper limit of normal (ULN) ($\leq 5 \times$ ULN if considered due to primary or metastatic liver involvement)
  - Total bilirubin $\leq 1.5 \times$ ULN
  - Alkaline phosphatase $< 2 \times$ ULN ($< 5 \times$ ULN if considered due to tumor)
  - Serum creatinine ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 40 mL/min by Cockcroft-Gault formula

    Glomerular filtration rate estimation:
    $\{(140 - \text{age}) \times (\text{weight [in kg]}) /$
    $(72 \times \text{serum creatinine [in mg/dL]})\} \times 0.85$ (if female)
- Male patients with prostate cancer who are receiving androgen blockade will be eligible for the study.

- Male patients must be willing to use acceptable methods of contraception. For additional inclusion criteria, please see the specific appendix for each study drug (Appendix 6– Appendix 10).
- Female patients of childbearing potential must agree to use acceptable methods of contraception. For additional inclusion criteria, please see the specific appendix for each study drug (Appendix 6–Appendix 10).

Additional inclusion criteria specific to the study drug to be used are contained in the appropriate appendices as follows:

- Alectinib (Appendix 10)

4.1.2 Exclusion Criteria

Patients in all treatment arms except atezolizumab who meet any of the following criteria will be excluded from study entry (**all** exclusion criteria for patients in the atezolizumab arm have been moved to Appendix 11 A11-4.1.2):

- Patients with hematologic malignancies
- Concurrent administration of any other anti-cancer therapy (except male patients with prostate cancer who are receiving androgen blockade):
  - Bisphosphonates and denosumab are allowed.
  - Most recent anti-cancer therapy ≤28 days or who have not recovered from the side effects, excluding alopecia or mild residual neuropathy. Patients with alopecia or mild residual neuropathy may be eligible after discussion with the Medical Monitor
  - Radiation therapy within ≤14 days
- Active or untreated brain metastases
  - Patients with treated brain metastases are eligible if they have minimal neurologic symptoms, evidence of stable disease (for at least 1 month) or response on follow-up scan, and require no corticosteroid therapy.
- History of carcinomatous meningitis
- Uncontrolled concurrent malignancy (early stage is allowed if not requiring active therapy or intervention)
- Pregnant or breastfeeding, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Any of the following cardiovascular events within 6 months prior to study entry: myocardial infarction, malignant hypertension, severe/unstable angina, symptomatic congestive heart failure, cerebral vascular accident, or transient ischemic attack
- Pulmonary embolism within 30 days prior to study entry
- History or presence of clinically significant ventricular or atrial dysrhythmia >Grade 2

  - Patients with chronic, rate-controlled atrial arrhythmias who do not have other cardiac abnormalities are eligible.
- Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results
- Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol

All patients must meet the additional exclusion criteria for individual study drugs, as provided in the appendices as follows:

- Alectinib (Appendix 10)

4.2 METHOD OF TREATMENT ASSIGNMENT

All patients will be assigned to a specific treatment cohort (see Appendix 6–11) based on a molecular abnormality previously established upon review of tumor tissue. For patients who have mutations in more than one pathway who could be eligible for more than one study drug, the treating physician will determine the first pathway to target after consultation with the medical monitors. Consideration should be given to enrolling the patient in the pathway with the highest variant allele frequency (VAF) mutation. The final choice of study pathway will be made following a discussion between the physician and patient regarding potential adverse events related to study treatments as part of the Informed Consent process. Patients are not permitted to receive concurrent treatment of multiple pathways in this study, but may re-enroll following progression on one therapy for another targeted pathway therapy, provided they meet inclusion criteria for that pathway. A 21-day washout period between the last dose of the first treatment regimen and the first dose of the next treatment regimen is required.

Prior to treatment determination, the patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. An interactive web response system (IWRS) vendor will be used to manage patient enrollment and tracking. Patients must be registered via the IWRS prior to the initiation of study treatment. Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via IWRS, prior to initiation of the new study treatment.

Redacted copies of molecular profile reports must be submitted to Sarah Cannon Development Innovations (SCDI) for review and approval prior to registration via IWRS.

Electronic data capture (EDC) will be used for this study (Section 7.2).

4.3 STUDY TREATMENT

Since there are slight differences in study design based upon the specific treatment received, please refer to the study design for each individual study treatment in the appendices as follows:

- Trastuzumab plus Pertuzumab (Appendix 6)
- Erlotinib (Appendix 7)
- Vemurafenib plus Cobimetinib (Appendix 8)
- Vismodegib (Appendix 9)
- Alectinib (Appendix 10)
- Atezolizumab (Appendix 11)

Details of each study treatment, recommended concomitant medication, and prohibited medications are also contained in the appendices.

A schema of the general study design is presented in Figure 1.

4.3.1 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (trastuzumab, pertuzumab, erlotinib, vemurafenib, cobimetinib, vismodegib, alectinib, and atezolizumab) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, using the IWRS 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 returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.2 Post-Trial Access to Study Drugs

The Sponsor will offer patients continued access to study drug that they received after study completion in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product (http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf).

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Permitted Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient from ≤7 days prior to the first dose of study drug to the end-of-treatment visit. All concomitant medications should be reported to the investigator.

Patients who use oral contraceptives or hormone-replacement therapy and do not have breast cancer may continue these medications under the supervision of their physician. Androgen blockage may be continued for male patients with prostate cancer. Other medications may be continued unless otherwise indicated in the specific study drug appendix.

Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain), is permitted provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion being irradiated is not a target lesion for response assessments, because that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1 by IRC). It is not a requirement to withhold atezolizumab during palliative radiotherapy.

Supportive care, including antiemetic medications, may be administered at the discretion of the investigator.

COVID-19 vaccinations are permitted at the discretion of the investigator (see Section A11-4.4.3 for additional vaccination information regarding patients taking atezolizumab). When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label.

Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such.

4.4.2 Prohibited Therapy

No other investigational therapy should be given to patients.

No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment, with the exception of palliative radiotherapy (see Section 4.4.1) and androgen blockage for male patients with prostate cancer. If such treatment is required, then the patient must first be withdrawn from the trial.

Additional excluded concomitant therapies are provided in the specific appendix for each study drug (see Appendix 6–11).

4.5 STUDY ASSESSMENTS

Please see Appendix 6–11 for the schedule of assessments performed during the study.

4.5.1 Definitions of Study Assessments

4.5.1.1 Informed Consent Forms and Screening Log

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

Sites will be required to submit limited pre-screening information for all patients being considered for enrollment into the atezolizumab arm. This information must be submitted to SCDI for approval for the patient to enter screening.

Redacted copies of molecular profile reports must be reviewed and approved by SCDI and the Sponsor to confirm that patients meet molecular eligibility criteria before registration via IWRS.

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via IWRS prior to initiation of the new study treatment.

4.5.1.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the first dose of study drug.

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

4.5.1.3 Tumor and Response Evaluations

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator using RECIST v1.1 (see Appendix 4).

As part of tumor assessment, standard practice physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Computed tomography (CT) scans should include chest, abdomen, and pelvis scans; additional scans may be obtained at the discretion of the investigator, based on the

location of measurable disease. At the investigator's discretion, CT scans may be repeated at any time if progressive disease (PD) is suspected.

4.5.1.4 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, serum chemistries, and pregnancy tests will be analyzed at the study site's local laboratory.

In addition, treatment-specific laboratory assessments will be performed as described in the specific appendix for each study drug (see Appendix 6–11).

Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, white blood cell count, and 3-part differential)
- Serum chemistries (sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen [BUN], creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase)
- Pregnancy test: all women of childbearing potential, including those who have had tubal ligation, will have a serum pregnancy test at screening. Patients who have a positive pregnancy test may not receive study drug. See Appendix 6 and Appendix 11 for pregnancy testing during treatment with pertuzumab/trastuzumab, vismodegib, and atezolizumab, respectively.
- Plasma samples for somatic tumor-specific genetic testing of ctDNA will be collected from all patients participating in the trial. These samples will be used for research purposes to identify biomarkers that correlate with treatment response or resistance and may be used for diagnostic assay development (Appendix 6–11).
- Additional molecular profiling results
  - If additional molecular profiling is done at the site while the patient is on study, the results should be reported in the eCRF and copies of the reports provided to the Sponsor
- Tumor tissue samples will be obtained to assess study objectives, support assay development and enable additional biomarker research. Methodologies used may include, but are not limited to WGS, WES, RNA sequencing, FISH, IHC, or RT-PCR and will be performed at selected CLIA-certified laboratories.
  - For all patients receiving trastuzumab/pertuzumab, see tissue requirements in A6-4.5.1.2
  - For all patients receiving atezolizumab, see tissue requirements in A11-4.5.1.2.1.
  - For patients in treatment arms other than trastuzumab plus pertuzumab and atezolizumab, collection of a sample of their archived tumor biopsy specimen (if available) is highly encouraged; please see Appendix 7 –11 for additional details or requirements.

  - On a case-by-case basis, residual material from local biomarker testing available at study sites or testing laboratories may be requested, as applicable
- For additional atezolizumab-specific assessments, see A11-4.5.1.2.1

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

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Biomarkers specimens, including residual material (e.g., slides, extracts) will be destroyed or returned within 5 years after the date of final closure of the clinical database. Archival tumor blocks, if provided, will be returned upon request. For sample handling procedures, storage conditions and shipment instructions, see the laboratory manual.

Based on increasing knowledge gained from data in this study and other studies, collection of any sample type may be stopped at any time if the data from the samples collected does not produce useful information.

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.

4.5.1.5 Patient-Reported Outcomes

Patient-reported outcomes will be assessed only for atezolizumab-treated patients enrolled under Version 6 of the protocol and later. See A11-4.5.1.2.2for the required assessments.

4.5.2 Screening and Pretreatment Assessments

Please see the specific appendix for each study drug (Appendix 6–11) for the required screening and pretreatment assessments.

4.5.3 Assessments During Treatment

Please see the specific appendix for each study drug (Appendix 6–11) for the assessments required during the selected treatment cohort.

4.5.4 End of Treatment

Please see the specific appendix for each study drug (Appendix 6–11) for evaluations required at the end-of-treatment (or safety) visit.

For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles.

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via IWRS prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

Patients with ongoing objective response or stable disease will continue therapy until tumor progression, occurrence of unacceptable toxicity, or other discontinuation criteria are met (see below).

Patients may be withdrawn from the study (see Section 4.6.1) or discontinued from study treatment (see Section 4.6.2). Patients who are withdrawn from the study and withdraw consent will not be followed. Patients who discontinue study treatment or withdraw from the study but do not withdraw consent will be followed for safety outcomes *as outlined in Section* 5.3.1. In addition, the Sponsor may decide to discontinue a specific cohort, the entire study, or a specific study site (see Section 4.6.3).

4.6.1 Patient Withdrawal from the Study

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Non-compliance (e.g., missed doses, visits)
- Patient is lost to follow-up

Every effort should be made to *follow-up on adverse events for* patients who withdraw from the study but have not withdrawn consent (see *Section* 5.3.1 for reporting instructions). The primary reason for withdrawal from the study should be documented on the appropriate electronic Case Report Form (eCRF). If a patient withdraws from the study, the investigator may ask the patient whether he/she wishes to allow continued collection of clinical outcome data in accordance with the informed consent signed by the patient. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Patient Discontinuation from Study Treatment

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

- Pregnancy
- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to study drug
- Patient requests to discontinue treatment, but does not withdraw consent
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (per investigator's discretion)

After discontinuation from protocol treatment, patients must be followed for adverse events (see Section 5.3.1 for reporting instructions).

See the specific appendix for each study drug (Appendix 6–11) for assessments that are to be performed for patients who prematurely discontinue study treatment.

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

4.6.3 Pathway, Cohort, Study, and Site Discontinuation

The Sponsor may close a specific study pathway or disease cohort at any time. Reasons for closure of specific study cohorts may include, but are not limited to, the following:

- Insufficient or slower than expected enrollment to that cohort
- The incidence or severity of adverse events in the cohort from this or other studies indicates a potential health hazard to patients.
- Steering Committee decision

If a cohort is closed for reasons other than safety, patients who are already enrolled will remain on treatment per protocol; however, no new patients will be enrolled to that cohort.

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.
- Data recording is inaccurate or incomplete, as judged by the Sponsor.

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

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 Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

All study drugs are approved and marketed for use in indications other than those being investigated in this study; these known safety profiles, which have been well characterized for approved indications, are included in the IB for each study drug. It is not anticipated that the safety profiles of the study drugs will differ markedly when the study drug is used in different tumor types; however, that cannot be completely ascertained. For that reason, the safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed in the specific appendix for each study drug (Appendix 6–11).

Guidelines for management of specific adverse events are provided in the specific appendix for each study drug (Appendix 6–11).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- 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., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (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 include the events listed below.

Adverse Events of Special Interest – All Study Drugs

- Cases of potential drug-induced liver injury (DILI) 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 5.3.5.6) and based on the following observations:
  - Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin >2 × ULN (of which ≥35% is direct bilirubin)
  - Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Adverse Events of Special Interest–Specific to Each Study Drug

Pertuzumab

- Asymptomatic decline in left ventricular ejection fraction (LVEF) requiring treatment or leading to discontinuation of trastuzumab and pertuzumab

Trastuzumab

- Congestive heart failure (symptomatic LVSD dysfunction)

Erlotinib

- Interstitial lung disease

Vemurafenib/Cobimetinib

- Serious retinopathy including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Any grade retinal vein occlusion (RVO)
- Symptomatic Heart Failure and/or Grade ≥2 left ventricular ejection fraction reduction
- Rhabdomyolysis
  - Includes Grade ≥3 elevations of creatine phosphokinase (CPK) in conjunction with other laboratory evidence (aldolase and urine myoglobin) and clinical presentation consistent with rhabdomyolysis (such as muscle pain, signs of renal failure, dark red or brown urine)
- Grade ≥3 hemorrhage event or any grade cerebral hemorrhage
- Grade ≥3 rash
- Events suggestive of DILI or other Grade ≥ 3 hepatotoxicity (see Section 5.3.5.6)
  - Grade ≥3 elevations of AST, ALT, serum bilirubin, gamma-glutamyl transferase (GGT), or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- AEs potentially associated with prolongation of cardiac repolarization (Grade ≥3 QT interval prolongation)
- Non-cutaneous squamous cell carcinoma
- Skin cancers
- Any new or worsening malignancies, including progression of RAS mutant malignancy, cutaneous squamous cell carcinoma (cuSCC), new primary melanoma, or basal cell carcinoma
- Grade ≥ 3 photosensitivity (when administered with vemurafenib)
- Gastrointestinal polyps
- Pneumonitis
- Grade ≥3 diarrhea

Vismodegib

- Grade ≥3 elevations of AST, ALT, serum bilirubin, GGT, or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- Pregnancy

Atezolizumab

- Pneumonitis
- Colitis

- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders, such as Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, influenza like illness, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- *Myelitis*
- *Facial paresis*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that adverse events (see treatment-specific guidelines in paragraph below) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For all patients except those in atezolizumab arm that enroll under Version 6 of the protocol or later, only significant AEs, defined as serious AEs (SAEs) (see Section 5.2.2), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be recorded in the Adverse Event eCRF.

For patients in the atezolizumab arm enrolling under Version 6 of the protocol or later, all adverse events will be recorded in the Adverse Event eCRF.

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 (Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug (for all patients except atezolizumab-treated patients enrolled under Version 6 of the protocol or later), adverse events (see Section 5.2.1), protocol-defined events of special interest (see Section 5.2.3), and serious adverse events (except those unequivocally related to disease progression), will be collected until 30 days (45 days for vismodegib) following the last administration of study treatment or study discontinuation/termination, whichever is later. For atezolizumab patients enrolled in Version 6 and later, 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, investigators should report only serious adverse events that are believed to be related to study drug treatment received while in the study (see Section 5.6).

See Section 5.5.1 for follow-up of adverse events that are ongoing at the end of study treatment.

Patients who re-enroll and receive treatment with another targeted-pathway therapy in this study following progression on one therapy will undergo a 21-day washout period between the last dose of the first treatment regimen and the first dose of the next treatment regimen. At the end of the 21-day washout, adverse event information will be collected for the previous therapy.

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 (v4.0) will be used for assessing adverse event severity for patients enrolled prior to Version 6 of the protocol.

The NCI CTCAE (v5.0) grading scale will be used for assessing adverse event severity for patients enrolled under Version 6 of the protocol or later. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale

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 (applicable for both v4.0 and 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 one's self, 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 or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

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

AE = adverse event.

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 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions (IV Trastuzumab/Pertuzumab Arm)

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Infusion-Related Reactions and Cytokine-Release Syndrome (Atezolizumab Arm)

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 specific diagnosis (e.g., "infusion-related reaction", "anaphylactic reaction") on the Adverse Event eCRF. Avoid ambiguous terms such as "systemic reaction." 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.

There may be significant overlap in signs and symptoms of IRRs and cytokine-release syndrome (CRS). In recognition of the challenges in clinically distinguishing between these two events, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 13.

Other Adverse Events

For adverse events other than infusion-related reactions, 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.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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.

5.3.5.3 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 of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

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

5.3.5.4 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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [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 if 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) 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).

5.3.5.7 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 cancer should be recorded only on the End of Treatment/Early Discontinuation eCRF. All other on-study deaths, regardless of

relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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").

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit and prior to the first treatment 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").

5.3.5.9 Lack of Efficacy or Worsening of Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using 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.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

- Hospitalization for respite care

- Planned hospitalization required by the protocol (e.g., for study 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 suffered 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

5.3.5.11 Patient-Reported Outcome Data (Atezolizumab Arm Only)

Adverse event reports will not be derived from PRO data and safety analyses will not be performed using PRO data. No attempt will be made to reconcile the findings from reports of treatment-related symptoms by the clinicians (NCI CTCAE) and from the patients (EORTC) given the different ways in which these two data sources are collected.

Although sites are expected to review the PRO data only for completeness, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.3.5.12 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm

- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

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). Regardless of whether they result in adverse events or not, all special situations associated with trastuzumab, pertuzumab, erlotinib, vemurafenib, cobimetinib, vismodegib, alectinib, and atezolizumab, should be recorded as described below in the Adverse Event eCRF:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

In addition, all adverse events resulting from special situations associated with trastuzumab, pertuzumab, erlotinib, vemurafenib, cobimetinib, vismodegib, alectinib, and atezolizumab, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the drug name and adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter drug name and the adverse 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

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.

5.4 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 drug:

- Serious adverse events (see Section 5.4.2)
- Adverse events of special interest (see Section 5.4.2)
- Pregnancies (see Section 5.4.3)

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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

To ensure the safety of study participants, access to the 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

The Investigator must report serious adverse events and adverse events of special interest on the applicable Sarah Cannon Safety form via secure e-mail connection or via fax immediately (within 24 hours) to the Innovations Safety Department:

Sarah Cannon Development Innovations Safety Department

Fax No.: 866-807-4325
Secure Email: CANN.SAE@SCRI-Innovations.com

Completing and submitting the Sarah Cannon Safety form does not take the place of the site entering information into the trial EDC. The site is still required to enter all event information onto the Adverse Event eCRF per study agreements and contracts.

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 the timeframe specified in Table 4 below after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form and fax cover sheet must be completed and faxed to Sarah Cannon Development Innovations Safety Department immediately (i.e., no more than 24 hours after learning of the pregnancy) using the fax numbers provided in Section 5.4.2. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study

drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. See Appendix 6 and Appendix 9 for additional information regarding follow-up of pregnancies in female patients exposed to trastuzumab/pertuzumab and vismodegib, respectively.

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 the timeframe specified in Table 4 below after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form and fax cover sheet must be completed and faxed to SCRI Development Innovations Safety Department immediately (i.e., no more than 24 hours after learning of the pregnancy) using the fax numbers provided in Section 5.4.2. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Clinical Trial Pregnancy Reporting Form and fax cover sheet with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. See Appendix 6 and Appendix 9 for additional information regarding follow-up of pregnancies in female partners of male patients exposed to trastuzumab/pertuzumab and vismodegib, respectively.

Table 4 Reporting Requirements for Pregnancies after the Last Dose of Study Drug

	Timeframe after the Last Dose of Study Drug	
Study Drug	Females	Males
Trastuzumab/Pertuzumab	7 months	7 months
Erlotinib	1 month	Not applicable
Vemurafenib/Cobimetinib	6 months	6 months
Vismodegib	24 months	3 months
Alectinib	1 week	3 months
Atezolizumab	5 months	Not applicable

5.4.3.3 Abortions

A spontaneous 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*).

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, initiation of another anti-cancer therapy, the patient is lost to follow-up, or the patient withdraws consent. This includes adverse events that are ongoing at the end of treatment. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from

hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period if the event is believed to be related to study drug treatment received while in the study.

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

Genentech Drug Safety Department

Fax No.: 650-238-6067

Email: usds_aereporting-d@gene.com

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:

- IB for the specific study drug
- Local prescribing information for the specific study drug

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

This is a broad study of patients whose tumors express molecular abnormalities of interest across all potential solid tumor types and lines of therapy (within the context of the inclusion/exclusion criteria). It is therefore not known which specific patient populations (tumor types and lines of therapy) will be studied within each pathway and

consequently pre-specifying safety and efficacy criteria is not feasible. This study will rely on the Study Steering Committee to develop safety and efficacy criteria for the tumor-pathway cohorts (cohorts will be identified during early accrual and criteria will be developed prior to review of efficacy outcomes). Details of criteria and statistical analyses will be provided in the Statistical Analysis Plan and the Study Steering Committee charter.

The efficacy and safety analyses will be performed on the treated study population, which includes all enrolled patients who receive at least one dose of study medication.

6.1 DETERMINATION OF SAMPLE SIZE

The primary goal of this trial is to evaluate the efficacy of these targeted agents across a broad range of tumor types. Except for the atezolizumab arm, treatment of up to approximately 75 patients in a specific tumor type with an individual targeted therapy (tumor-pathway) cohort will allow estimation of the response rate to treatment. For rarer tumor/disease pathway combinations (e.g., HER2+ salivary, biliary, bladder etc.), enrollment may be limited to up to approximately 25 patients. With 25 patients, the margin of error (defined as one-half the width of the confidence interval) does not exceed 19.6% for a 95% confidence interval.

For the atezolizumab arm, up to approximately 70 patients with tTMB ≥10 and <16 mutations/Mb as determined by the FoundationOne or FoundationOne CDx test will be enrolled, with the expectation that up to approximately 50 patients will be IRC-evaluable. Once 50 IRC-evaluable patients with tTMB ≥10 and <16 mutations/Mb have been enrolled, given potential variations in mutations/Mb calling between FoundationOne / FoundationOne CDx and other assays, patients with ≥10 and <16 mutations/Mb from a non-FoundationOne / non-FoundationOne CDx assay will be allowed to continue to enroll, provided there is sufficient tissue available for a retrospective FoundationOne CDx test.

Furthermore, for the atezolizumab arm, up to approximately 200 patients with tTMB ≥16 mutations/Mb as determined by the FoundationOne or FoundationOne CDx test (local or by central re-testing) will be enrolled, with the expectation that up to approximately 150 will be IRC-evaluable.

With 180 patients, the margin of error does not exceed 7.5% for a 95% confidence interval. With 150 patients, the margin of error does not exceed 8.0% for a 95% confidence interval. With 75 patients, the margin of error does not exceed 11.3% for a 95% confidence interval. With 50 patients, the margin of error does not exceed 13.9% for a 95% confidence interval.

Additionally, for the atezolizumab arm, enrollment will be restricted for specific subpopulations of patients with tTMB ≥16 mutations/Mb who would be evaluable by IRC as follows:

- For the subpopulation with NSCLC, mUC, or melanoma, enrollment will be capped at up to approximately 30 patients (for all 3 tumor types combined, up to approximately 10 patients each).
- For the subpopulation with co-occuring tTMB ≥16 mutations/Mb and MSI-H, enrollment will be capped at up to approximately 20 patients (regardless of tumor type).

The total number of patients enrolled in each (tumor-pathway) cohort will vary depending on the feasibility of enrollment (mutation rates within tumor types) and interim analysis decisions. The specific tumor-pathway cohorts and their sample size are therefore difficult to anticipate in this study setting. It is expected that a total of approximately 765 patients will be enrolled in this study. Based on the results of interim analyses, as well as ongoing enrollment feasibility evaluations, the total target patient accrual to this study may be amended in collaboration with the Steering Committee.

6.2 EFFICACY ANALYSES

6.2.1 Final Efficacy Analysis

In this study, it is expected that approximately 20–75 patients will enroll in a disease and treatment cohort (i.e., specific tumor type treated with one of the study treatments) except for the atezolizumab arm. *The final analysis will occur after all patients in a specific tumor and study treatment cohort have completed study assessments.* The ORR and DCR will be estimated and the 70% and 95% confidence intervals will be constructed using exact binomial distribution.

It is anticipated that some (tumor-pathway) cohorts may reach less than 20–30 patients at the end of the study due to the rarity of the specific mutation in that disease. For these smaller (tumor-pathway) cohorts, ORR and DCR with confidence intervals will be calculated, although confidence intervals will be wider. Response rates (ORR and DCR) by study treatments will also be estimated across the various tumor types (where appropriate) along with 95% confidence intervals.

Median PFS and median DOR and their associated 95% confidence intervals, as well as 1-year OS, will be estimated using the Kaplan-Meier method. Descriptive analyses of safety and efficacy for each study arm (pathway summaries) will also be summarized across the various tumor types where appropriate.

6.2.2 Primary Efficacy Endpoint

The primary endpoint for this study will be ORR. The ORR is defined as the proportion of patients whose best response is a complete response (CR) or partial response (PR). In determining the ORR in this trial, only patients with measurable disease will be

included. ORR will be determined by RECIST v1.1 for all patients. Confidence intervals at both 70% and 95% nominal levels will be reported. The specific ORR endpoints are listed below:

- For all tumor-pathway cohorts: ORR, as assessed by the investigator
- For atezolizumab-treated patients with tTMB ≥16 mutations/Mb (as assessed by FoundationOne or FoundationOne CDx): ORR, as assessed by IRC

6.2.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints for each disease cohort will consist of DCR, PFS, 1-year OS, and DOR, which are listed and defined below. For the atezolizumab arm only, additional secondary endpoints will also be evaluated and are outlined below:

- DCR is defined as the proportion of patients whose best response is CR, PR, or stable disease maintained for more than 4 months. DCR will be summarized in the same fashion as the primary efficacy endpoint.
- PFS is defined as the time from first study treatment to the first occurrence of disease progression as assessed by the investigator, or death from any cause (whichever occurs first). The PFS will be estimated using the Kaplan-Meier method.
- 1-year OS is defined as the 1-year survival rate from the date of first treatment, based on the Kaplan-Meier estimate.
- DOR is defined as the time from the date of first documented response (CR or PR) to the time of disease progression or death from any cause, whichever occurs first among patients who have experienced a complete or partial response.
- ORR, as assessed by an IRC, for atezolizumab-treated patients with bTMB ≥16 mutations (as determined by FoundationOne Liquid CDx). ORR will be determined using RECIST v1.1 criteria.
- ORR, as assessed by the investigator, for atezolizumab-treated patients with tTMB ≥10 and <16 mutations/Mb (as assessed by FoundationOne or FoundationOne CDx): ORR will be determined using RECISTv1.1 criteria.

6.2.4 Exploratory Biomarker Endpoints

The exploratory biomarker endpoints for this study are as follows:

- All disease cohorts: relationship between somatic tumor-specific mutations, identified through NGS performed on ctDNA extracted from blood, and efficacy as well as other biomarker endpoints related to the evolution of disease
- For selected disease cohorts: relationship between supplementary molecular profiling data and somatic tumor-specific biomarkers, or markers of the tumor microenvironment as well as the relationship between supplementary molecular profiling data and efficacy or other biomarker endpoints related to the evolution of disease

6.3 SAFETY ANALYSES

Evaluation of safety will be based on summaries of adverse events (AEs) (including deaths) for the safety population.

For all patients except atezolizumab-treated patients enrolled under Version 6 of the protocol or later, only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) occurring from the first treatment until 30 days (45 days for vismodegib) after the last dose of study treatment, will be summarized by preferred term and NCI CTCAE v4.0 (patients enrolled prior to Version 6 of the protocol) or NCI CTCAE v5.0 (patients enrolled under Version 6 and later versions).

For the atezolizumab-treated patients enrolled under Version 6 of the protocol or later, all AEs occurring from the first treatment until 90 days after the last dose of study treatment will be summarized by preferred term NCI CTCAE v5.0.

Deaths reported during the study treatment, and those reported during the 30-day follow-up (45 days for vismodegib, 90 days for atezolizumab) after end of treatment will be summarized.

6.4 BIOMARKER ANALYSES

Biomarker analyses for all treatment arms on collected tumor tissue may include but are not limited to the assessment of genomic alterations (e.g. central re-testing, co-mutations, MSI status) and characterization of the tumor microenvironment using WGS, WES, FISH, IHC, RNA sequencing, and/or RT-PCR.

For patients in the atezolizumab arm without tTMB assessed by FoundationOne or FoundationOne CDx, mandatory tissue samples will be used to centrally re-test tTMB by FoundationOne CDx. Assay agreement for tTMB using local assays results (not determined by Foundation Medicine Inc.) and FoundationOne CDx may be determined. Biomarker analyses on remaining mandatory samples, optional tissue samples or residual material may include but are not limited to the characterization of the tumor microenvironment or assessment of neoantigen load using WGS, WES, FISH, IHC, RNA sequencing, and/or RT-PCR. Plasma samples will be used to determine bTMB by FoundationOne Liquid CDx and is needed to assess the association of bTMB with clinical outcome as well as concordance with tTMB at baseline.

Plasma samples of all treatment arms will be used to determine mutation calls and variant allele frequencies will be studied over time and correlated with clinical outcome using NGS.

For all treatment arms, descriptive statistics of biomarker data will include means, medians, ranges, and SDs, as appropriate. For categorical analyses, frequency distributions will be tabulated as appropriate. Biomarker data in blood and tumor tissue will be used for additional subgroup analyses, studied over time (if available) and to explore potential relationships with efficacy, safety, PK, and immunogenicity.

6.5 PHARMACOKINETIC AND IMMUNOGENICITY ANALYSES

Atezolizumab serum concentration data (C_{min}) will be tabulated and summarized for each respective cycle at which pharmacokinetics are to be measured. Descriptive statistics of PK concentrations will include means, medians, ranges, and SDs, as appropriate.

Additionally, serum samples will be used to evaluate the formation of ADAs and the potential relationships of such ADA (anti-atezolizumab) formation with other outcome measures (e.g., PK, efficacy, safety) may be assessed.

Due to the need for baseline samples, pharmacokinetic and immunogenicity analyses will only be performed for atezolizumab-treated patients enrolled under Version 6 of the protocol and later.

6.6 PATIENT-REPORTED OUTCOME ANALYSES

PROs of patient functioning, HRQoL, symptom severity and bother with adverse events will be assessed using the EORTC item library. Due to the need for baseline assessments, PRO analyses will only be performed for atezolizumab-treated patients enrolled under Version 6 of the protocol and later.

Rate of completion of the questions, summary statistics (mean, SD, median, and range, rate of missing data) of linear transformed scores will be reported at each timepoint for all scales according to the EORTC scoring manual guidelines. The mean change of the linear transformed scores from baseline (and 95% CI with use of the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment of scales will be provided. In addition, time to deterioration or improvement in selected scales such as quality of life (global health status [GHS]) and functioning (role functioning [RF], physical function [PF]) will be documented according to event defined in the Statistical Analysis Plan (SAP).

6.7 HANDLING OF MISSING DATA

ORR and DCR: If a patient has started treatment but does not have any post-baseline tumor assessment (e.g., due to early withdrawal from the study), the patient will be considered as a non-responder in the ORR and DCR analyses.

PFS: Data for patients without disease progression or death will be censored at the date of the last tumor assessment (or, if no tumor assessments were performed, after the baseline visit, at the date of first treatment).

1-year OS: If the 1-year survival status of the patient, defined as 365 days after the date of first treatment, cannot be ascertained, the date will be censored at the date of last contact (clinic visit or telephone) with the patient.

Valid tTMB results from FoundationOne or FoundationOne CDx: If a patient with IRC evaluable-disease does not have a valid tTMB result determined by FoundationOne or FoundationOne CDx, the patient will be excluded from efficacy analyses being performed in the FoundationOne or FoundationOne CDx tTMB selected patient population.

6.8 INTERIM ANALYSES

In this trial, patients with a variety of tumor types will be enrolled on each drug or drug combination, since eligibility depends primarily on the existence of key mutations. It is anticipated that the efficacy of these targeted agents will vary depending on the tumor type and primary site.

Therefore, for all treatment arms except atezolizumab, an interim analysis will be conducted when a cohort of 12 patients with a specific tumor type has been treated with one of the targeted therapies has a baseline and post-baseline scan, or has come off trial for an adverse event.

For the subpopulation with NSCLC, mUC, and melanoma, enrollment will be capped at approximately 10 patients (for all 3 tumor types combined, up to approximately 3 patients each).

These interim analyses will be utilized to identify (tumor-pathway) cohorts in which treatment is ineffective (i.e. futility analysis), either due to lack of efficacy or safety considerations, so that further accrual to such a cohort can be stopped.

For these interim analyses, ORR and DCR will be the efficacy endpoints considered. Any PFS or DOR data available will also be considered, although short follow-up may limit interpretation. Guidelines to assist in decision-making will be developed in collaboration with the study Steering Committee and will be tailored to the specific tumor types and the evolving treatment landscape. These guidelines will be provided in the study Steering Committee charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO), Sarah Cannon Development Innovations, will be responsible for

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

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using 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.

The eCRF completion guidelines will help identify appropriate responses that may be specific for this study. For example, inclusion/exclusion identifiers (such as 1, 1a, 1b) are listed in these guidelines to aid in completing the eCRF.

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 listed on the FDA Form 1572.

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records,

clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section *7.5*.

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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 (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the U.S. 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 EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Forms for each of the (tumor-pathway) cohorts (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 specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to 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.

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.

In addition, patients whose disease progresses on one study treatment and is being considered for another treatment in this study must be re-consented with the most current version of the Consent Form, for that treatment.

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 U.S., 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.

In the event that a patient withdraws his/her consent and/or HIPAA authorization, the study site and authorized recipients of patient information may continue to use and disclose patient information collected prior to the withdrawal of patient consent/authorization.

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 *9.4*).

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

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

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

8.5 FINANCIAL DISCLOSURE

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

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, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL VIOLATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by Genentech, Inc., a member of the Roche Group. The CRO (SCRI Development Innovations) will perform study and safety monitoring as well as data management.

9.5 PUBLICATION 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, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/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 made available upon request.* For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

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.

9.6 PROTOCOL AMENDMENTS

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

A protocol amendment will be provided if treatment with another marketed product is added to this study.

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
Eastern Cooperative Oncology Group Performance Status (ECOG PS) Criteria

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 2
New York Heart Association Classification of Cardiac Disease

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 3
Guidelines for Women of Childbearing Potential and Male Patients

For guidelines on women of childbearing potential and male patients, please refer to the specific appendix for each study drug:

- Trastuzumab plus Pertuzumab (Appendix 6)
- Erlotinib (Appendix 7)
- Vemurafenib plus Cobimetinib (Appendix 8)
- Vismodegib (Appendix 9)
- Alectinib (Appendix 10)
- Atezolizumab (Appendix 11)

For reporting requirements for pregnancies, please see Section 5.4.3 in the main body of the protocol.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST 1.1): Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). In addition, lymph nodes in the pelvis must measure ≥2 cm in greatest diameter to be considered target lesions. At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft-tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography that includes a ruler to estimate the size of the lesion is suggested.

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine whether substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

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

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

<u>TUMOR RESPONSE EVALUATION</u>

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent

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

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge whether a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

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

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements

are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

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

- Complete response (CR): Disappearance of all target lesions
  - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
  - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  - The appearance of one or more new lesions is also considered progression.
  - Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

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

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions
  - The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

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

Bone Only Disease: Since bone lesions are not considered measurable, patients with bone only disease will be evaluated for progression only. Progression is defined as the appearance of new lytic lesions or other new bone destruction thought to be related to cancer by X-ray, MRI, or CT scan or a bone event requiring intervention (surgery) if not associated with trauma or other obvious cause. Changes in bone scan or ^{18}F-sodium fluoride (NaF) PET scan should not be used to define progression. Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. The appearance of new lesions on bone scan or ^{18}F-NaF PET scan may constitute progressive disease if associated with clinical symptoms suggestive of disease progression. The occurrence of a pathologic fracture at a site previously recognized bone disease may constitute progressive disease if not associated with trauma or other obvious cause. Bone pain requiring radiation will constitute progressive disease. Increase in pain at a site of previously recognized bone disease may constitute progressive disease if it is persistent and not associated with other obvious cause.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal; that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For

example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

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

Table 1
Timepoint Response: Patients with Target Lesions
(with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2
Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

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

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, since this equates with the case being not evaluable at that timepoint.

Table 3
Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

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

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal, in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The

objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and Table 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (e.g., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
Methods for Evaluation of Genetic and Other Alterations in Genes of Interest

Gene	Linked Study Drug	Method [a]	Material	Molecular Alteration/ Mutation(s) of Interest	References
HER2 (ERBB2)	Trastuzumab Pertuzumab	In situ hybridization	• Tissue	• HER2/CEP17 signal ratio >2.0 or HER2 gene copy number>6	Wolff et al. 2013.
HER2 (ERBB2)	Trastuzumab Pertuzumab	IHC	• Tissue	• 3+ score	Wolff et al. 2013.
HER2 (ERBB2)	Trastuzumab Pertuzumab	PCR + Sanger sequencing NGS [b]	• Tissue and/ or blood [d]	• Increased HER2 gene copy number	Grasso et al. 2015 Starczynski J et al. 2013; Ross JS et al. 2018.
ALK	Alectinib	FISH (Vysis ALK break apart FISH assay or comparable)	• Tissue	• ALK gene rearrangements	
ALK	Alectinib	NGS	• Tissue and/ or blood [d]	• ALK gene rearrangements • Putative activating non-synonymous mutations, short nucleotide variants, or indels in and around the ALK kinase domain (amino acid 1062-1311) • ALK copy number gain	Forbes et al. 2015; Mossé et al. 2008; Hallberg and Palmet 2013; Bresler et.al. 2014; Murugan and Xing 2011; Bavi et al. 2013.
ALK	Alectinib	IHC	• Tissue	Melanoma only (not applicable to other tumor types): • Increased expression of the ALK protein	Wiesner et al. 2015.

Appendix 5
Methods for Evaluation of Genetic and Other Alterations in Genes of Interest (cont.)

Gene	Linked Study Drug	Method [a]	Material	Molecular Alteration/ Mutation(s) of Interest	References
ALK	Alectinib	RT-PCR or RNA sequencing	• Tissue	Melanoma only (not applicable to other tumor types): • Presence of ALK^{ATI} transcript (exon 1-19, intron 19, exon 20-29)	Wiesner et al. 2015.
tTMB	Atezolizumab	NGS	• Tissue	• Elevated tTMB ≥10 mutations/Mb as determined using any CLIA validated assay. Once 50 IRC-evaluable patients with tTMB ≥ 10 and < 16 mutations/Mb have been enrolled, patients will be allowed to enroll if they have a tTMB result ≥ 16 mutations/Mb as determined using any CLIA validated assay. However, given potential variations in mutations/Mb calling between FoundationOne / FoundationOne CDx and other assays, patients with ≥10 and <16 mutations/Mb from a non-FoundationOne / non-FoundationOne CDx assay will be allowed to continue to enroll, provided there is sufficient tissue available for a retrospective FoundationOne CDx test.	Frampton et al 2016; George et al. 2016.

Appendix 5
Methods for Evaluation of Genetic and Other Alterations in Genes of Interest (cont.)

Gene	Linked Study Drug	Method [a]	Material	Molecular Alteration/ Mutation(s) of Interest	References

Note: Formalin-fixed, paraffin-embedded blocks or frozen tissues of surgical specimens, fine needle biopsies, or pleural/peritoneal effusions are considered adequate tissue specimens for enrollment screening.

ALK=anaplastic lymphoma kinase; ALK^{ATI}=ALK-alternative transcription initiation; dMMR=deficient mismatch repair; EGFR=epidermal growth factor receptor; FISH=fluorescence in situ hybridization; HER1=human epidermal growth factor 1; HER2=human epidermal growth factor 2; IHC=immunohistochemistry; MMR=mismatch repair; MSI=microsatellite instability; MSI-H=MSI-high; NGS=next generation sequencing; PCR=polymerase chain reaction; PTCH=protein patched homolog; RT-PCR=real-time polymerase chain reaction; SMO=smoothened; tTMB=tissue tumor mutational burden.

[a] Determined by assays performed at a CLIA-certified laboratory.

[b] Results generated from NGS include variant allelic frequency (VAF); 5% is the lower limit of VAF of the mutation that will allow for treatment in a specific drug cohort.

[c] Molecular testing results obtained from blood samples are encouraged to be confirmed in tissue within the first month of the patient being on study.

[d] Molecular testing results obtained from blood samples MUST be accompanied by respective tissue testing result confirming patient eligibility within the first month of the patient being on study. Note that an archival/new tissue biopsy should be submitted for analyses addressing exploratory biomarker objectives in addition.

Appendix 6
Trastuzumab plus Pertuzumab for Patients with Cancers Characterized by HER2 Overexpression, Amplification, or HER2-Activating Mutation

(Treatment Arm Closed to Enrollment)

Treatment of patients with solid tumors that are characterized by human epidermal growth factor 2 (HER2) overexpression or amplification, or HER2-activating mutation is part of the clinical trial outlined in the main protocol. This appendix contains details and study requirements that are specific to treatment with trastuzumab plus pertuzumab, including:

A6-4 MATERIALS AND METHODS

A6-4.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol. Listed here are additional requirements specific to treatment with trastuzumab plus pertuzumab.

A6-4.1.1 Additional Inclusion Criteria

- Patients must have the following tumor types:
  - Biliary cancer
  - Salivary cancer
  - Bladder cancer
- Patients with solid tumors that have HER2 overexpression or amplification as identified by assays performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.
  - Assays using in situ hybridization (fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization [CISH]) must indicate the presence of gene

amplification with a HER2/CEP17 ratio of >2.0 or HER2 gene copy number >6.0.

- Assays using IHC must indicate a score of 3+.
- Assays using next generation sequencing (NGS) or real-time polymerase chain reaction (RT-PCR) must identify HER2 gene copy number gain.
- For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- In cases where multiple assays are done, HER2 positivity by any of the testing methodologies would make the patient eligible as long as eligibility criteria are fulfilled.
- For further information regarding specific testing methodologies and allowable identified mutations, see Appendix 5.

- Left ventricular ejection fraction (LVEF) >50% or above the lower limit of the institutional normal range, whichever is lower
- Availability of an archival or new pretreatment tissue sample is required if molecular testing was not performed by Foundation Medicine. The tissue sample must be submitted within 4 weeks after enrollment (refer to A6-4.5.1.2 for tissue requirements).
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use an acceptable contraceptive method during the treatment period and for at least 7 months after the last dose of study treatment

  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 following are acceptable contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

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

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

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

A6-4.1.2 Additional Exclusion Criteria

- Previous treatment with any HER2-targeted therapy

For exploratory biomarker analysis and tumor tissue sample requirements, see A6-4.5.1.2 .

A6-4.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (Section 4.2).

A6-4.3 STUDY TREATMENT

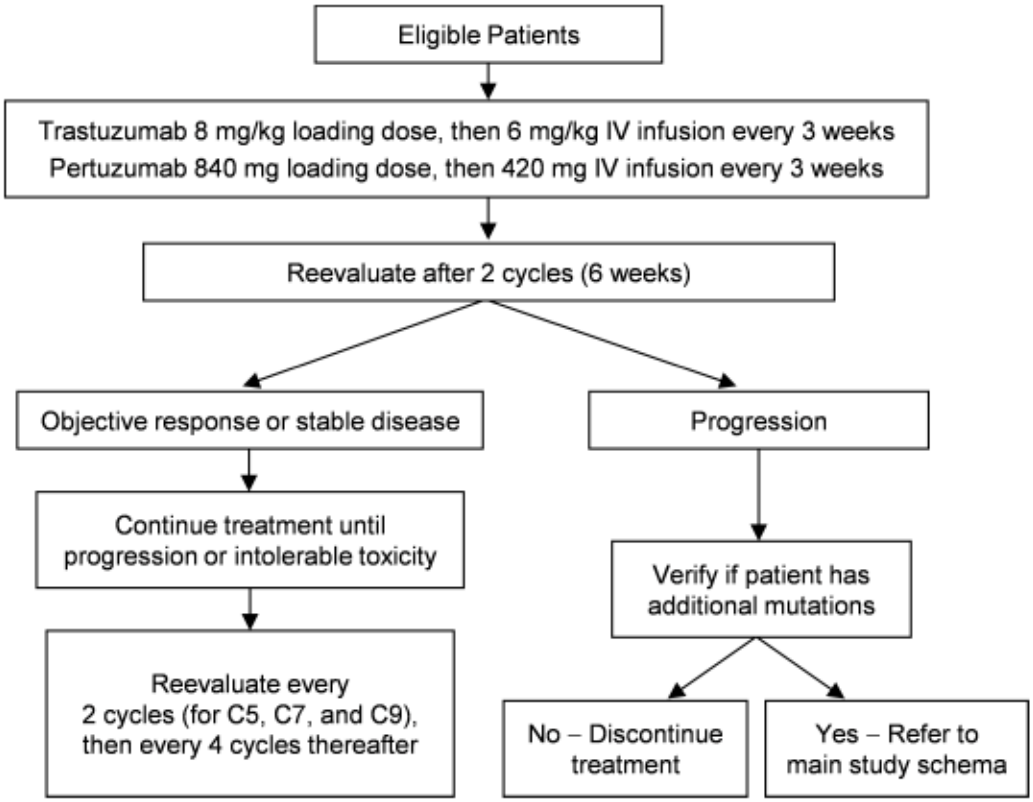
All patients will receive treatment with pertuzumab plus trastuzumab, given intravenously (IV) in cycles of 21 days (3 weeks) duration. A schema of the study design is presented in A6-Figure 1.

All patients will receive:

- Trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg, given by IV infusion every 3 weeks.
- Pertuzumab 840 mg IV loading dose, followed by 420 mg, given by IV every 3 weeks.
- The order of administration of trastuzumab and pertuzumab is according to investigator preference.
- Both antibodies will be infused according to the U.S. Package Insert (USPI).
- No routine premedications are required; however, patients who experience infusion-related symptoms may be premedicated as per standard institutional practice for subsequent infusions.

For additional information regarding the dosage and administration of trastuzumab and pertuzumab, please see Section A6-4.3.1b and Section A6-4.3.2b, respectively, of this appendix.

A6-Figure 1: Study Schema: Trastuzumab plus Pertuzumab



C=cycle.

A6-4.3.1 Trastuzumab (Herceptin®)

a. Formulation

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder for IV administration. Each vial of trastuzumab contains 440 mg of trastuzumab, 9.9 mg of L-histidine HCl, 6.4 mg of L-histidine, 440 mg of α,α-trehalose dihydrate, and 1.8 mg of polysorbate 20, USP. Reconstitution with 20 mL of the supplied bacteriostatic water for injection (BWFI) USP, containing 1.1% benzyl alcohol as a preservative, yields 21 mL of a multidose solution containing 21 mg/mL trastuzumab, at a pH of ~6. Effective 31 May 2019, the formulation of trastuzumab will change. Each single-dose vial of trastuzumab will deliver 150 mg trastuzumab, 136.2 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl monohydrate, 2.2 mg L-histidine, and 0.6 mg polysorbate 20. Reconstitution with 7.4 mL of sterile water for injection yields a solution containing 21 mg/mL trastuzumab that delivers 7.15 mL (150 mg trastuzumab), at a pH of approximately 6.

b. Dosage, Administration, and Storage

The 8 mg/kg loading dose of trastuzumab should be administered over 90 (±10) minutes. DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. Trastuzumab

dosing will be based on the patient's baseline weight measurement. Weight will be measured on Day 1 of every 3-week treatment cycle. In case of a ≥10% change in weight, the trastuzumab dose should be re-calculated using the new weight. For the first infusion (Cycle 1), patients should be observed for 60 minutes from the end of the infusion for fever and chills, or other infusion-related reactions. If Cycle 1 is tolerated, then Cycle 2 and subsequent Q 21 day doses of 6 mg/kg of trastuzumab may be administered over 30 (±10) minutes, and patients will be observed as shown in A6-Table 1. All infusion related symptoms must have resolved before pertuzumab (if trastuzumab was given first) is given or the patient is discharged. Patients who experience infusion-related symptoms may be premedicated as per standard institutional practice for subsequent infusions.

With the exception of changes in trastuzumab dose due to a ≥10% change in weight from the baseline weight measurement, no changes in trastuzumab dosing are allowed at any time. Trastuzumab will be held or discontinued in case of unacceptable toxicity.

Instructions for the administration of trastuzumab are listed below.

A6-Table 1 Infusion Time and Post-Infusion Observation Period for Trastuzumab

Infusion	Trastuzumab Dose (mg/kg)	Infusion Time (min)[a]	Post-Infusion Observation Period (min)[a]
1st infusion	8	90	60
2nd infusion	6	30	30
3rd and subsequent infusions	6	30	None

[a] After Cycle 1, ONLY shorten infusion and post-infusion observation times if the prior dose was well-tolerated.

Storage

Vials of trastuzumab are stable at 2°C–8°C (36°F–46°F) prior to reconstitution. Do not use beyond the expiration date stamped on the vial. A vial of trastuzumab reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C–8°C (36°F–46°F), and the solution is preserved for multiple uses. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved sterile water for injections (not supplied) is used, the reconstituted trastuzumab solution should be used immediately and any unused portion must be discarded. **DO NOT FREEZE TRASTUZUMAB THAT HAS BEEN RECONSTITUTED**.

The solution of trastuzumab for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for injection, USP, may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted trastuzumab has been shown to be

stable for up to 24 hours at room temperature 15°C–25°C; however, since diluted trastuzumab contains no effective preservative the reconstituted and diluted solution should be stored refrigerated (2°C–8°C).

c. Dosage Modification

Trastuzumab is well tolerated by most patients. If Grade 3–4 toxicity attributed to trastuzumab occurs, further dosing should be held until the toxicity improves to ≤Grade 1. Trastuzumab should be restarted at full dose. If Grade 3–4 toxicity recurs, trastuzumab should be discontinued. Patients who are benefiting from therapy may continue treatment with pertuzumab, at the discretion of their treating physician. For information regarding dosage modification for pertuzumab, see Section A6-4.3.2c.

d. Management of Toxicities

Management of specific trastuzumab-related toxicities is discussed below.

Hematologic Toxicity and Neutropenic Infections

In clinical trials, an increased incidence of anemia was observed in patients receiving trastuzumab plus chemotherapy compared with patients receiving chemotherapy alone. Most of these episodes of anemia were mild or moderate in intensity and were reversible. None of these events resulted in discontinuation of trastuzumab therapy.

In clinical trials, the incidences of moderate to severe neutropenia and febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared with those who received chemotherapy alone. In the post-marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving trastuzumab and myelosuppressive chemotherapy. However, in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined. The effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated.

Management of Hematologic Toxicities with Trastuzumab

Care should be taken to carefully monitor the patient's hematologic status throughout the course of the trial. Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and should be in accordance with the American Society of Clinical Oncologists guidelines.

Trastuzumab Overdosage

There has been no instance of overdosage of trastuzumab in human clinical trials. Single doses of higher than 500 mg of trastuzumab have not been tested.

Cardiac Dysfunction

Signs and symptoms of cardiac dysfunction were observed in a number of women who received trastuzumab alone or in combination with chemotherapy, most often anthracycline-based treatment. Cardiac dysfunction was observed most frequently among patients who received trastuzumab plus adriamycin/cyclophosphamide chemotherapy (28%), compared with those who received adriamycin/cyclophosphamide alone (7%), trastuzumab plus paclitaxel (11%), paclitaxel alone (1%), or trastuzumab alone (7%). Severe disability or fatal outcome due to cardiac dysfunction was observed in approximately 1% of all patients.

In contrast to the irreversible nature of anthracycline-induced cardiomyopathy, the signs and symptoms of trastuzumab-induced cardiac dysfunction usually responded to treatment. Complete and partial responses were observed among patients with cardiac dysfunction. The risk appears to be independent of tumor response to therapy. Analysis of the clinical database for predictors of cardiac dysfunction revealed only advanced age and exposure to an anthracycline as possible risk factors. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy, often including discontinuation of trastuzumab. In many cases, patients were able to resume treatment with trastuzumab. In a subsequent study using weekly paclitaxel and trastuzumab as first-line treatment for metastatic breast cancer, the observed incidence of serious cardiac dysfunction was 3% (N=95) (Seidman et al. 2001). Since the occurrence of cardiac dysfunction in the trastuzumab plus chemotherapy trial was an unexpected observation, no information is available regarding the most appropriate method for monitoring cardiac function in patients receiving trastuzumab.

Significant advances in the understanding and treatment of congestive heart failure (CHF) have been made in the past several years, with several new drugs demonstrating the ability to improve cardiac function. Patients who develop symptoms of CHF while on trastuzumab should be treated according to the Heart Failure Society of America (HFSA) guidelines (HFSA 2010).

Since **pertuzumab** is also associated with a risk for cardiac dysfunction, the management of cardiac safety for patients receiving both drugs in the trial, as outlined in the next section, applies to both drugs. For additional information regarding the risk of cardiotoxicity for pertuzumab, see Section A6-4.3.2d.

Management of Cardiac Safety. All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either a multiple-gated acquisition (MUGA) scan or an echocardiogram (ECHO) prior to entry into the study. Only patients with normal LVEF should be entered into this study. While receiving treatment, all patients will have regular monitoring of LVEF with MUGA or ECHO (every 12 weeks or as clinically indicated).

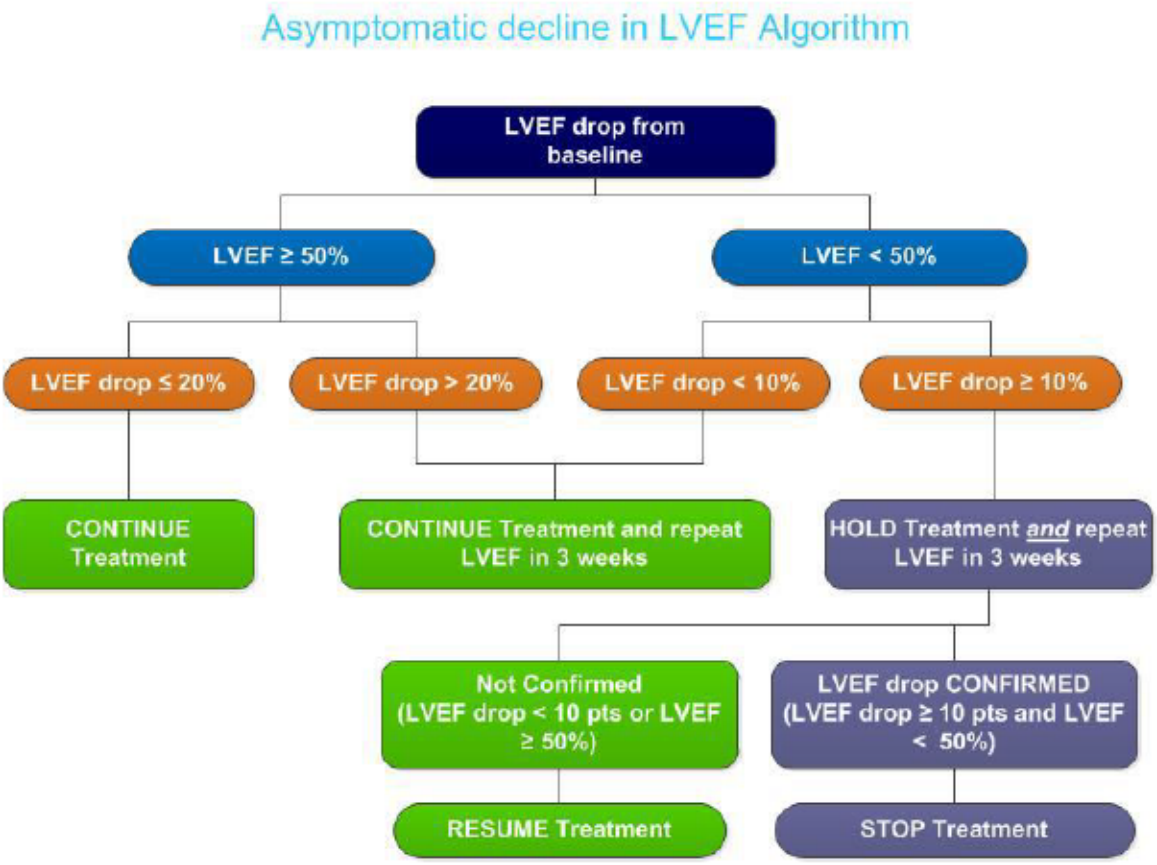
During the course of therapy with trastuzumab and pertuzumab patients should be monitored for signs and symptoms of heart failure (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The diagnosis must be confirmed using the same method used to measure LVEF at baseline (either ECHO or MUGA).

Management of Symptomatic Cardiac Changes. Patients who develop signs and symptoms of heart failure NCI CTCAE v4.0 Grade 2, 3, or 4 should have trastuzumab and pertuzumab held and should receive treatment for heart failure as prescribed by the HFSA (e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed; HFSA 2010). Consideration should be given to obtaining a cardiac consultation. LVEF should be reassessed after 3 weeks (using the same method of measurement).

If the symptoms of heart failure resolve with treatment, and cardiac function (as measured by ECHO or MUGA) improves, trastuzumab and pertuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from HER2-targeted treatment, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If trastuzumab and pertuzumab are restarted, continued surveillance with noninvasive measures of LVEF (MUGA or ECHO) will continue per protocol.

Management of Asymptomatic Decreases in LVEF. If routine LVEF measurements document asymptomatic LVEF decreases during treatment, patient management should follow guidelines outlined in A6-Figure 2.

A6-Figure 2: Left Ventricular Ejection Fraction Algorithm



LVEF = left ventricular ejection fraction.

e. Trastuzumab Warnings and Precautions

Infusion Reactions to Trastuzumab

During the first infusion with trastuzumab, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent trastuzumab infusions. These symptoms may be treated as per standard institutional practice.

Serious Infusion-Associated Events with Trastuzumab

Serious adverse reactions to trastuzumab infusion, including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress, can be serious and/or potentially fatal. Most of these events have occurred either during or shortly after the start of the first trastuzumab infusion. Severe or moderate infusion-related symptoms may be managed by slowing or stopping the trastuzumab infusion, and implementing supportive therapy with oxygen, beta agonists, antihistamines, or corticosteroids.

If Grade 3 or Grade 4 toxicity occurs during the post-infusion observation period, the patient must be evaluated for a minimum of 1 hour from the time the toxicity was first observed until the resolution of any severe symptoms.

Patients who have an infusion-associated adverse event with trastuzumab should receive prophylactic treatment with antihistamines and/or corticosteroids before all subsequent trastuzumab infusions. Please refer to the Herceptin® USPI for specific prophylactic pre-medications that are recommended.

Other Trastuzumab-Related Toxicity

In addition to infusion-related toxicity, some patients have reported abdominal pain, indigestion, diarrhea, nausea, vomiting, loss of appetite and dehydration. Allergic reactions have also been reported. One patient in a large research study developed antibodies to trastuzumab.

A6-4.3.2 Pertuzumab (Perjeta®)

a. Formulation

Pertuzumab is provided 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).

b. Dosage, Administration, and Storage

Withdraw the indicated volume of pertuzumab from the vial and add to a 250-cc IV bag of 0.9% sodium chloride injection. Gently invert the bag to the mix solution. DO NOT SHAKE VIGOROUSLY. Visually inspect the solution for particulates and discoloration prior to administration. The entire volume within the bag should be administered as a continuous IV infusion. The volume contained in the administration tubing should be completely flushed using a 0.9% sodium chloride injection.

The solution of pertuzumab for infusion diluted in PVC or non-PVC polyolefin bags containing 0.9% sodium chloride injection may be stored at 2°C–8°C (36°F–46°F) for up to 24 hours prior to use. Diluted pertuzumab has been shown to be stable for up to 24 hours at room temperature (2°C–25°C). However, since pertuzumab contains no preservative, the aseptically diluted solution should be stored refrigerated (2°C–8°C) for no more than 24 hours.

A rate-regulating device may be used for all pertuzumab infusions. When the study drug IV bag is empty, 50 mL of 0.9% sodium chloride injection may be added to the IV bag or an additional bag will be hung, and the infusion may be continued for a volume equal to that of the tubing to ensure complete delivery of pertuzumab.

Administration of pertuzumab should be performed in a setting with emergency equipment and staff who are trained to monitor medical situations and respond to medical emergencies. The initial dose of pertuzumab will be administered over

60 minutes and patients will be monitored for a further 60 minutes following the completion of the infusion for any adverse effects. The infusion should be slowed or interrupted if the patient experiences infusion-related symptoms. If infusion-related symptoms occur, patients will be monitored until complete resolution of signs and symptoms. If the infusion is well tolerated, subsequent doses may be administered over 30 minutes, and patients will be observed for a further 30 minutes (as shown in A6-Table 2) for infusion-related symptoms. All infusion-related symptoms must have resolved before the patient is discharged. Patients who experience infusion-associated symptoms may subsequently be premedicated as per standard institutional practice.

A6-Table 2 Infusion Time and Post-Infusion Observation Period for Pertuzumab

Infusion	Pertuzumab Dose (mg)	Infusion Time (min) [a]	Post-Infusion Observation Period (min) [a]
1st infusion	840	60	60
2nd infusion and subsequent infusions	420	30	30

[a] After Cycle 1, ONLY shorten infusion and post infusion observation times if the prior dose was well tolerated.

Infusion should be stopped in patients who develop dyspnea or clinically significant hypotension (defined per investigator discretion). Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction or acute respiratory distress syndrome should not receive additional pertuzumab.

Should extravasation of the study drug during the infusion, the following steps should be taken:

- Discontinue the infusion.
- Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent.
- If a significant volume of the study drug infusion remains, restart the infusion at a more proximal site in the same limb or on the other side.

Storage

Vials of pertuzumab must be placed in a refrigerator 2°C–8°C (36°F–46°F) immediately upon receipt to ensure optional retention of physical and biochemical integrity and should remain refrigerated until immediately prior to use. DO NOT FREEZE and DO NOT SHAKE the pertuzumab vial. Protect from light.

c. Dosage Modification

Pertuzumab is well tolerated by most patients. If Grade 3–4 toxicity attributed to pertuzumab occurs, further dosing should be held until the toxicity improves to

≤ Grade 1. Pertuzumab should be restarted at full dose. If Grade 3–4 toxicity recurs, pertuzumab should be discontinued. Patients who are benefiting from therapy may continue treatment with trastuzumab, at the discretion of their treating physician. For information regarding dosage modification for trastuzumab, see Section A6-4.3.1c.

Management of specific pertuzumab-related toxicities is discussed below.

d. Pertuzumab Warnings and Precautions

Infusion-Associated Reactions

An infusion reaction was defined in the randomized trial for metastatic breast cancer as any event described as hypersensitivity, anaphylactic reaction, acute infusion reaction, or cytokine release syndrome occurring during an infusion or on the same day as the infusion. The initial dose of pertuzumab was given the day before trastuzumab and docetaxel to allow for the examination of pertuzumab-associated reactions. On the first day, when only pertuzumab was administered, the overall frequency of infusion reactions was 13.0% in the pertuzumab-treated group and 9.8% in the placebo-treated group. Less than 1% were Grade 3 or 4. The most common infusion reactions (≥ 1.0%) were pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting.

During the second cycle when all drugs were administered on the same day, the most common infusion reactions in the pertuzumab-treated group (≥ 1.0%) were fatigue, dysgeusia, hypersensitivity, myalgia, and vomiting.

In the randomized trial, the overall frequency of hypersensitivity/anaphylaxis reactions was 10.8% in the pertuzumab-treated group and 9.1% in the placebo-treated group. The incidence of Grade 3–4 hypersensitivity/anaphylaxis reactions was 2% in the pertuzumab-treated group and 2.5% in the placebo-treated group according to NCI CTCAE v3.0. Overall, 4 patients in pertuzumab-treated group and 2 patients in the placebo-treated group experienced anaphylaxis.

Observe patients closely for 60 minutes after the first infusion and for 30 minutes after subsequent infusions of pertuzumab. If a significant infusion-associated reaction occurs, slow or interrupt the infusion and administer appropriate medical therapies as per standard institutional practice. Monitor patients carefully until complete resolution of signs and symptoms. Consider permanent discontinuation in patients with severe infusion reactions.

Risk of Cardiotoxicity

Pertuzumab is directed at the HER2 receptor and is associated with a risk of cardiac dysfunction.

In pertuzumab single-agent Phase II studies, a fall in LVEF of ≥ 10% to a LVEF value of < 50% was observed in 7% of patients who had a post-baseline LVEF assessment. Nine of these patients had received prior anthracycline treatment. Overall, three symptomatic

cardiac failure events have been reported in approximately 550 patients treated with pertuzumab across all studies. Two of these cases occurred in patients with metastatic breast cancer who had received prior anthracyclines.

Patients with significant cardiac disease or baseline LVEF below 50% are not eligible for this study. Risk factors for pertuzumab-associated cardiac dysfunction are not known at this time. The risk of cardiac dysfunction should be carefully weighed against the potential benefit in patients who have received prior anthracyclines.

Since pertuzumab and trastuzumab have overlapping potential cardiac toxicity, the management of cardiotoxicity in this study arm should consider both treatments. For additional information regarding cardiac dysfunction for trastuzumab or pertuzumab, see Section A6-4.3.1d.

Embryo-Fetal Toxicity (for Trastuzumab or Pertuzumab)

There are no clinical studies of trastuzumab or pertuzumab in pregnant women. Immunoglobulin G1 (IgG1) is known to cross the placental barrier. Studies in animals have resulted in oligohydramnios, delayed renal development, and death. Advise patients of these risks and the need for effective contraception (see additional inclusion criteria in Section A6-4.1.1).

It is not known whether trastuzumab or pertuzumab is excreted in breast milk. As maternal IgG1 is excreted in milk and either monoclonal antibody could harm infant growth and development, women should be advised to discontinue nursing during pertuzumab or trastuzumab therapy and not to breastfeed for at least 7 months following the last dose of either monoclonal antibody.

Follow-Up of Pregnancies

Infants born to female patients or female partners of male patients exposed to trastuzumab/pertuzumab must be followed for 1 year after birth. Additional information will be requested by the Sponsor at specific timepoints during and after the pregnancy (i.e., at the end of the second trimester, 2 weeks after expected date of delivery, and 3, 6, and 12 months of the infant's life).

Most Common Adverse Reactions

The most common adverse reactions (>30%) seen with pertuzumab in combination with trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy. The most common NCI CTCAE (v 3.0) Grade 3–4 adverse reactions (>2%) were neutropenia, febrile neutropenia, leukopenia, diarrhea, peripheral neuropathy, anemia, asthenia, and fatigue.

A6-4.4 CONCOMITANT AND EXCLUDED THERAPIES

A6-4.4.1 Concomitant Therapy

Please refer to the main body of the protocol (Section 4.4.1) for concomitant therapies allowed.

A6-4.4.2 Excluded Therapy

No additional therapies are excluded for patients receiving trastuzumab and pertuzumab.

A6-4.5 STUDY ASSESSMENTS

All patients should visit the study center on the days specified in A6-Table 3 of this appendix. Molecular profiling reports must be seen and reviewed by the investigator prior to proceeding with other study-specific assessments. The complete schedule of assessments for patients receiving trastuzumab and pertuzumab is contained in the study flowchart of this appendix. Baseline medical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), complete blood counts (CBC), and comprehensive metabolic profile (CMP) should be done ≤21 days prior to initiation of treatment. If the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1, they do not have to be repeated on Day 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and tumor markers (if applicable) to document measurement of disease must be performed ≤4 weeks prior to initiation of treatment.

A6-4.5.1 Definitions of Study Assessments

A6-4.5.1.1 General Study Assessments

See Section 4.5.1 in the main body of the protocol for descriptions of the assessments.

A6-4.5.1.2 Trastuzumab plus Pertuzumab-Specific Laboratory Samples

The following laboratory samples are required for patients receiving trastuzumab/pertuzumab:

- Tumor Tissue Samples:
  - For all patients receiving trastuzumab/pertuzumab, collection of an archival or new pretreatment tissue sample is required if molecular testing was not performed using FoundationOne (Foundation Medicine Inc). Tissue requirements are as follows:
    - Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)
    - Submission of 15, but at least 10 serial, unstained, positively-charged glass slides prepared from FFPE tumor blocks at 4um thickness is required.
    - Presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should

have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.

– Optional: at disease progression. Tissue requirements are as follows:

A biopsy may be collected at disease progression to enable exploratory biomarker analyses. If multiple lesions are available, the same tumor lesion should be biopsied at all timepoints, if feasible.

Although any tumor tissue material can be submitted, it is encouraged to submit tissue as follows:

- Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)
- Ideally, submission of 15, but not less than 10, serial, unstained, positively charged glass slides prepared from FFPE tumor blocks and 4μm thickness
- Presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.

A6-4.5.2 Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of HER2 overexpression, or amplification (should occur prior to obtaining other study-specific assessments). For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- ECOG PS
- Measurement of LVEF (MUGA or ECHO)
- CBC, including 3-part differential and platelets
- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Confirm availability of an archival or new pretreatment tissue sample (refer to A6-4.5.1.2 for tissue requirements)
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

A6-4.5.3 Assessments during Treatment

Patients will visit the study center once every 3 weeks on the day of each scheduled treatment (±72 hours). Protocol treatments will continue until tumor progression or intolerable toxicity occurs. The following assessments will be performed:

a. Day 1 of Every Cycle

- Adverse event (AE) evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).

b. Day 1 of Cycles 1and 3

- Plasma biomarker collection

c. Day 1 of Cycles 1, 2, 3, and 7; and Every Three Cycles Thereafter

- CBC, including 3-part differential and platelets
- CMP

d. Day 1 of Cycles 3 and 5

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)

e. Day 1 of Cycle 4 and Every Three Cycles Thereafter

- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

f. Day 1 of Cycle 5

- Measurement of LVEF (use the same test that was used for baseline measurement). MUGA or ECHO will be repeated every 12 weeks, or as clinically indicated, during treatment.

g. Day 1 of Cycle 7

- Tumor markers (only if clinically indicated)

- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

h. Day 1 of Cycle 9 and Every Four Cycles Thereafter

- Measurement of LVEF (use the same test that was used for baseline measurement). MUGA or ECHO will be repeated every 12 weeks, or as clinically indicated, during treatment.

i. As Clinically Indicated

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- *PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)*
- *CT scan or MRI of brain (only if abnormal at baseline)*

A6-4.5.4 End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of trastuzumab and pertuzumab. The following assessments will be conducted at the follow-up visit:

- AE evaluations
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- CBC, including 3-part differential and platelets
- CMP
- Urine or serum pregnancy test – Any positive urine pregnancy test must be confirmed by a serum pregnancy test. *A urine or serum pregnancy test must be performed at the treatment discontinuation visit and then every 3 months thereafter until 7 months post-discontinuation of study treatment.*
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline and necessary to document response to treatment)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles.
- At disease progression, an optional FFPE tissue sample may be submitted for exploratory research, if available.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

A6-4.6 PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

A6-4.7 PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST (TRASTUZUMAB AND PERTUZUMAB)

Please refer to Section 5.2.3 in the main body of the protocol for protocol-defined adverse events of special interest.

Appendix 6
Trastuzumab plus Pertuzumab for Patients with Cancers Characterized by HER2 Overexpression, Amplification, or HER2-Activating Mutation (cont.)

A6-Table 3: Trastuzumab and Pertuzumab Study Flowchart

	Pre-Treatment	Trial Treatment							
		All Cycles	Reassessments						
Assessments	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 4, Day 1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	Cycle 9, Day 1 (and Every 4 Cycles After) (±3 Days)	Cycle 13, Day 1 (and Every 6 Cycles After) (±3 Days)	*As Clinically Indicated* [b]	End of Treatment Safety Follow-Up [c]
Tests and Observations									
Informed consent [d]	x								
Obtain/review molecular profiling report/ pathology report [e]	x								
Medical history	x								
ECOG PS	x								
LVEF (ECHO or MUGA)	x		x [f] [Cycle 5, Day 1 only]			x [f]			
Adverse event evaluation [g]		x							x
Laboratory Evaluations									
CBC, 3-part differential, and platelets	x	x [Day 1 of Cycles 1, 2, 3 & 7; and every 3 cycles afterward]							x
Plasma biomarkers		x [Day 1, Cycle 1 and 3 only]							

Appendix 6
Trastuzumab plus Pertuzumab for Patients with Cancers Characterized by HER2 Overexpression, Amplification, or HER2-Activating Mutation (cont.)

Assessments	Pre-Treatment	Trial Treatment							End of Treatment Safety Follow-Up [c]
		All Cycles	Reassessments						
	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 4, Day 1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	Cycle 9, Day 1 (and Every 4 Cycles After) (±3 Days)	Cycle 13, Day 1 (and Every 6 Cycles After) (±3 Days)	*As Clinically Indicated* [b]	
CMP [h]	x	x [Day 1 of Cycles 1, 2, 3 & 7; and every 3 cycles afterward]							x
Pregnancy test [i]	x			x					*x* [j]
Optional molecular profiling results [k]		x							
Archival tumor sample [l]	x [l]								x [l]
Staging									
Tumor markers [m]	x		x		x			*x*	
CT scan of chest, abdomen, pelvis [n]	x		x [o]		x [o]			*x* [o]	x [o]
PET scan or bone scan [n]	x [m]				x [p]			*x* [p]	
Head CT or MRI scan [n]	x [q]				x [r]			*x* [r]	
Treatment									
Trastuzumab +Pertuzumab		x	x	x	x	x	x		

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography.

Appendix 6
Trastuzumab plus Pertuzumab for Patients with Cancers Characterized by HER2 Overexpression, Amplification, or HER2-Activating Mutation (cont.)

[a] The medical history, ECOG PS, CBC, and CMP should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment. ECHO/MUGA for LVEF assessment should be performed ≤4 weeks prior to initiation of treatment

[b] *Assessments should be performed when clinically indicated.*

[c] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles.

[d] Informed consent must be obtained prior to performing any trial-related screening assessments.

[e] Confirmation of HER2 overexpression or amplification (see Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[f] Measurement of LVEF (use the same test that was used for baseline measurement). MUGA or ECHO will be repeated every 12 weeks, or as clinically indicated, during treatment.

[g] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[h] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[i] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

[j] At the treatment discontinuation visit and then every 3 months thereafter until 7 months post-discontinuation of study treatment.

[k] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[l] Submission of an archival or new pretreatment tissue sample is required for all patients where molecular testing was not performed by Foundation Medicine. For other patients, submission of an archival or new pretreatment tissue sample is requested. The tissue sample must be submitted within 4 weeks after enrollment (refer to A6-4.5.1.2 for tissue requirements). At disease progression, an optional FFPE tissue sample may be submitted for exploratory research, if available.

[m] Only if clinically indicated.

[n] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle. For patients with CRC and HER2 amplification or overexpression, with a PR or CR as assessed by the investigator, scans should be submitted for central review.

[o] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles.

[p] Only if abnormal at baseline and if necessary to determine response to treatment.

[q] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[r] Only if abnormal at baseline.

Appendix 7
Erlotinib in Patients with EGFR-Activating Mutations

(Treatment Arm Closed to Enrollment)

Treatment of patients with solid tumors that harbor epidermal growth factor receptor (EGFR)-activating mutations is part of the clinical trial outlined in the main protocol. This appendix contains details and study requirements that are specific to treatment with erlotinib, including:

A7-4 MATERIALS AND METHODS

A7-4.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol. Listed here are additional requirements specific to treatment with erlotinib.

A7-4.1.1 Additional Inclusion Criteria

- Patients with solid tumors that harbor EGFR-activating mutations
- EGFR positivity as determined by next generation sequencing (NGS) or real time polymerase chain reaction (RT-PCR) performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory will be accepted.
  - Standard assays using polymerase chain reaction (PCR)- or next generation sequencing (NGS)-based technology for the identification of EGFR mutations in DNA derived from formalin-fixed paraffin-embedded human tumor tissue or in circulating tumor DNA derived from plasma samples which identify the presence of somatic mutations in exons 18, 19, and 21 of the EGFR gene will be allowed.
  - Assays using NGS of genes with known or potentially clinically relevant alterations or analysis by RT-PCR must identify clinically activating mutations (those with major coding disruptions resulting in an amino acid change that is likely to be detrimental to protein function, including premature stop codons or frameshift mutations early in the coding region).

  - For information regarding specific testing methodologies and allowable identified mutations, see Appendix 5.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use an acceptable contraceptive method during the treatment period and for at least 1 month after the last dose of study drug

  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 following are acceptable contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  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.

A7-4.1.2 Additional Exclusion Criteria

- Non-small cell lung cancer (NSCLC) or pancreatic cancer identified by exon 19 deletions or exon 21 L858R substitution mutations
- EGFR amplifications in the absence of EGFR-activating mutations
- Cancers with exon 20 mutations
- Previous treatment with erlotinib or any other EGFR inhibitor
- Inability to swallow pills
- Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude absorption of erlotinib

A7-4.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (Section 4.2).

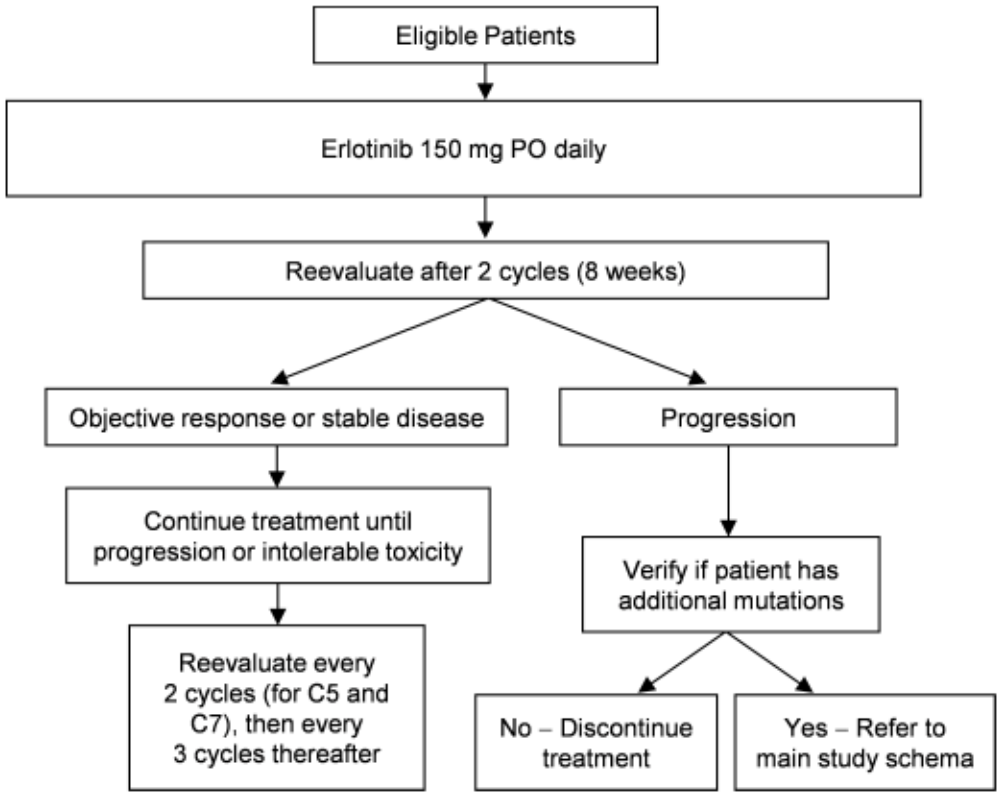
A7-4.3 STUDY TREATMENT

All patients will receive treatment with erlotinib, given at a daily dose of 150 mg orally (PO) in cycles of 28 days (4 weeks) duration. A schema of the study design is presented in A7-Figure 1.

All patients will receive:

- Erlotinib 150 mg PO daily
- No routine premedications are required.

A7-Figure 1: Study Schema: Erlotinib



C = cycle; PO = orally.

A7-4.3.1 Erlotinib (Tarceva®)

Erlotinib is a human EGFR Type 1/EGFR tyrosine kinase inhibitor. The mechanism of clinical anti-tumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with EGFR. Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

a. Formulation

The pharmaceutical preparations of erlotinib are formulations containing the hydrochloride salt. Erlotinib will be supplied as tablets containing erlotinib hydrochloride equivalent to 150 mg of erlotinib. All tablets are round, white, film-coated, bi-convex tablets without markings.

Erlotinib tablets will be supplied in blue-white, high-density polyethylene bottles of 30 tablets each.

Additional information regarding erlotinib can be found in the Tarceva® U.S. Package Insert.

b. Dosage, Administration, and Storage

Erlotinib tablets should be taken at approximately the same time each morning. Each erlotinib dose should be taken with up to 200 mL (approximately 1 cup or 8 oz) of water, and should be taken 1 hour before or 2 hours after ingestion of food. Erlotinib should not be taken with grapefruit or grapefruit juice. The entire dose must be taken at one time. Erlotinib tablets must be taken whole; they must not be crushed, broken, or dissolved. If a patient inadvertently does not take the erlotinib dose in the morning, he/she may take that day's erlotinib dose any time up to noon that same day. However, if a patient misses taking his/her scheduled erlotinib dose and is unable to take the missed erlotinib dose on the same day, the missed dose will not be "made up." If vomiting occurs after taking erlotinib, the patient should be instructed **not** to retake the dose. Patients should take the next scheduled dose of medication on the following day. If vomiting persists, the patient should contact the study doctor.

Storage

Erlotinib tablets should be stored at room temperature, not above 25°C (77°F).

c. Dosage Modification

The administration of erlotinib may be delayed to assess or treat adverse events (AEs). A single dose reduction (to 100 mg PO daily) is allowed. Once a dose level reduction has occurred, the dose level may not be re-escalated.

Dose Modifications Due to Hematologic Toxicity

Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Treatment on Day 1 of any cycle will proceed if blood counts demonstrate absolute neutrophil count (ANC) ≥1000/μL and platelets ≥75,000/μL.

A7-Table 1: Dose Modifications for Hematologic Toxicity

Day 1 Blood Counts	Erlotinib
ANC≥1000/μL; Platelets≥75,000/μL	No dose modification
ANC<1000/μL; Platelets<75,000/μL	Delay dose until ANC≥1000/μL and platelets≥75,000/μL Resume erlotinib at a dose of 100 mg PO daily
Neutropenic fever (ANC<1000/μL+Temperature≥101°F (38.5°C)	
1st incidence	Delay dose until episode resolves with treatment Resume erlotinib at a dose of 100 mg PO daily
2nd incidence	Discontinue treatment

ANC=absolute neutrophil count; PO=orally.
Note: Erlotinib should be discontinued if hematologic toxicity does not resolve (ANC≥1000/μL and platelets≥75,000/μL) within 14 days.

Dose Modifications Due to Non-Hematologic Toxicity

If Grade 3 or 4 non-hematologic toxicity (other than nausea, vomiting) occurs, treatment with erlotinib should be held, and should be resumed according to A7-Table 2 as soon as the toxicity resolves.

A7-Table 2: Dose Modification of Erlotinib for Grade 3 or Grade 4 Non-Hematologic Toxicity

Toxicity (Grade)	Action	Erlotinib Dose Reduction
Grade 3 1st occurrence [a]	Hold until recovery to ≤Grade 1, then resume treatment with a dose reduction to 100 mg daily	100 mg PO daily
Grade 4 1st occurrence [a]	Hold until recovery to ≤Grade 1, then resume treatment with a dose reduction of one dose level	100 mg PO daily, unless Grade 4 skin toxicity, in which case erlotinib must be discontinued

PO=orally.

[a] If Grade 3 or 4 recurs after erlotinib has been reduced to 100 mg PO daily, erlotinib should be discontinued.

Patients experiencing diarrhea, nausea/vomiting, erlotinib skin toxicity, or hypertension should first have recommended management/prophylaxis. Erlotinib dose reduction should occur only if Grade 3/4 toxicity persists/recurs. Erlotinib must be **discontinued** if Grade 4 skin toxicity occurs.

Diarrhea

Diarrhea should be treated with standard medications (e.g., loperamide) to avoid dose modifications or interruption, if possible. No dose modifications will be made with Grade 1 or 2 diarrhea.

If Grade 3 or 4 diarrhea develops, treatment should be interrupted, and maximal anti-diarrheal management should be instituted. When diarrhea improves to ≤Grade 1, erlotinib should be re-introduced without a dose reduction, with prophylactic loperamide management.

Nausea/Vomiting

Nausea/vomiting should be managed with standard antiemetic therapy.

Skin Toxicity

Skin toxicity may take the form of dry skin, rash, acneiform eruption, or hair or nail changes. Prophylactic treatment of the skin may prevent or reduce skin toxicity. The patient should be encouraged to use an alcohol-free, emollient cream applied twice a day to the entire body as soon as the patient starts therapy with erlotinib.

Patients who develop skin toxicity and are symptomatic should be treated with topical therapy such as hydrocortisone cream or clindamycin gel. If needed, oral minocycline or oral doxycycline may be combined with the topical therapy. A topical immunomodulating cream such as Elidel could also be considered. For more severe rash, oral corticosteroids may be beneficial. Patients who fail to respond to these measures may have the dose of erlotinib interrupted or reduced.

Other Toxicities

Erlotinib dosing should be discontinued for any severe toxicity that does not respond to treatment.

d. Erlotinib Warnings and Precautions

Interstitial Lung Disease

There have been infrequent reports of serious interstitial lung disease (ILD), including fatal events, in patients receiving erlotinib for the treatment of NSCLC and other advanced solid tumors. In the event of acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, study drug should be interrupted pending diagnostic evaluation. If ILD is diagnosed, study drug should be permanently discontinued and appropriate treatment instituted as necessary.

Hepatic Toxicity

Treatment with erlotinib should be used with extra caution in patients with total bilirubin $>3\times$ the upper limit of normal (ULN). Patients with hepatic impairment (total bilirubin >ULN or Child-Pugh A, B, and C) should be closely monitored during therapy with erlotinib. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range.

Elevated INR and Potential Bleeding

International Normalized Ratio (INR) elevations and infrequent reports of bleeding events, including gastrointestinal (GI) and non-GI bleedings, have been reported in clinical studies (some associated with concomitant warfarin administration). Patients taking warfarin or other coumarin-derivative anti-coagulants should be monitored for changes in prothrombin time or INR.

Renal Failure

Cases of acute renal failure or renal insufficiency (including fatalities), with or without hypokalemia, have been reported. Some of these cases were secondary to severe dehydration due to diarrhea, vomiting, and/or anorexia, while others were confounded by concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (e.g., pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other pre-disposing conditions, including advanced age), erlotinib therapy should be interrupted, and

appropriate measures should be taken to intensively re-hydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients who are at risk of dehydration.

Bullous and Exfoliative Skin Disorders

Bullous, blistering, and exfoliative skin conditions have been reported with the use of erlotinib, including very rare cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be discontinued in patients who develop severe bullous, blistering, or exfoliating conditions.

Gastrointestinal Perforation

Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which has been observed uncommonly. Some cases had a fatal outcome.

Patients receiving corticosteroids or nonsteroidal anti-inflammatory drugs, and patients who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop GI perforation.

Ocular Disorders

Very rare cases of corneal perforation or ulceration have been reported during the use of erlotinib. Other ocular disorders, including abnormal eyelash growth, keratoconjunctivitis sicca, or keratitis have been observed with erlotinib treatment, and are known risk factors for corneal perforation/ulceration. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Metabolism and Drug Interactions

Erlotinib is both protein bound (92% to 95% in humans) and metabolized in the liver by CYP3A4 and, to a lesser extent, CYP1A2, and in the lungs by CYP1A1. CYP3A4 inhibitors or a combined CYP3A4 and CYP1A2 inhibitor increase erlotinib plasma concentrations. Avoid concomitant use. If not possible, reduce erlotinib dose. A potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 and CYP1A2 inhibitors/inducers. For patients who are being concomitantly treated with a potent CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe adverse events. CYP3A4 inducers decrease erlotinib plasma concentrations. Avoid concomitant use. If not possible, increase erlotinib dose. For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered. Caution should be used when administering or taking erlotinib with ketoconazole and other strong CYP3A4 inhibitors (such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole). Alternate treatments lacking CYP3A4 inducing activity should be considered when using erlotinib. Erlotinib clearance can be induced by smoking via CYP1A2 induction. Cigarette smoking and

CYP1A2 inducers decrease erlotinib plasma concentrations. Avoid concomitant use. If not possible, increase erlotinib dose. Grapefruit juice is a CYP3A4 inhibitor that interferes with the metabolism of erlotinib. Therefore, consumption of grapefruit or grapefruit juice should be avoided during erlotinib treatment.

Aqueous solubility of erlotinib is dependent on pH with increased solubility at a pH less than 5; maximal solubility occurs at a pH of approximately 2. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure (area under the concentration–time curve, AUC) and maximum concentration observed (C_{max}) by 46% and 61%, respectively. There was no change in time to maximum concentration (T_{max}) or half-life. Therefore, drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for the loss of exposure.

Drugs that increase gastric pH decrease erlotinib plasma concentrations. For proton pump inhibitors avoid concomitant use if possible. For H-2 receptor antagonists, take erlotinib 10 hours after H-2 receptor antagonist dosing. For use with antacids, separate dosing by several hours.

In addition, altered coagulation parameters and bleeding have been reported in patients receiving erlotinib alone and in combination with other chemotherapeutic agents and concomitant warfarin-derivative anticoagulants. The mechanism for these alterations is still unknown. When warfarin is co-administered with erlotinib (any time after Day 5), INR, and prothrombin time should be closely monitored, and the anticoagulant dose should be adjusted as clinically indicated.

A7-4.4 CONCOMITANT AND EXCLUDED THERAPIES

A7-4.4.1 Concomitant Therapy

Refer to the main body of the protocol (Section 4.4.1) for concomitant therapies allowed.

A7-4.4.2 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.
- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial.
- Concomitant treatment with drugs that are strong inducers or inhibitors of the CYP3A4 enzymes should be avoided if possible. If possible, patients who are taking such agents should be switched to other agents that do not share CYP3A4 inhibition/induction.

A7-4.5 STUDY ASSESSMENTS

All patients should visit the study center on the days specified in A7-Table 3 of this appendix. Molecular profiling reports must be seen and reviewed by the investigator prior to proceeding with other study-specific assessments. The complete schedule of assessments for patients receiving erlotinib is contained in the study flowchart of this appendix. Baseline medical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), complete blood counts (CBCs), comprehensive metabolic profile (CMP) and electrocardiogram (ECG) should be done ≤21 days prior to initiation of treatment. If the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1, they do not have to be repeated on Day 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and tumor markers to document measurement of disease must be performed ≤4 weeks prior to initiation of treatment.

A7-4.5.1 Descriptions of Study Assessments

Refer to the main body of the protocol (Section 4.5.1) for details.

A7-4.5.2 Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of EGFR-activating mutation (should occur prior to obtaining other study-specific assessments)
- Medical history
- ECOG PS
- ECG, QTc interval measurement
- CBC, including 3-part differential and platelets
- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis
- PET scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening

assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

A7-4.5.3 Assessments During Treatment

Patients will visit the study center once every 4 weeks (±72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 7, Day 1, subsequent visits will be every 12 weeks, with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1

- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3

- Adverse event (AE) evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP

c. Day 1 of Cycle 3

- Plasma biomarker collection

d. Day 1 of Cycles 3 and 5

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)
- Review study drug compliance with patient

e. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or other protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP

- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

A7-4.5.4 End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of erlotinib. The following assessments will be conducted at the visit:

- Plasma biomarker collection
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

A7-4.5.5 Follow-Up Assessments

Please refer to the main body of the protocol for the follow-up assessments.

A7-4.6 PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

A7-4.7 PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST (ERLOTINIB)

Please refer to Section 5.2.3 in the main body of the protocol for protocol-defined adverse events of special interest.

Appendix 7
Erlotinib in Patients with EGFR-Activating Mutations (cont.)

A7-Table 3: Erlotinib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
Tests and Observations							
Informed consent [e]	x						
Obtain/review molecular profiling report/ pathology report [f]	x						
Medical history	x						
ECOG PS	x						
ECG, QTc interval measurement	x [g]						
Adverse event evaluation (all cycles) [h]		x	x	x	x		
Study drug compliance review [i]		x	x	x	x		
Survival status							x
Laboratory Evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP [j]	x	x		x	x		
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x		
Pregnancy test [k]	x						
Optional molecular profiling results [l]		x					
Optional archival tumor sample	x [m]						

Appendix 7
Erlotinib in Patients with EGFR-Activating Mutations (cont.)

Assessments	Pre-Treatment	Trial Treatment				Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)	End of Treatment Safety Follow-Up [b]	Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
Staging							
Tumor markers [n]	x		x	x	x	x	
CT scan of chest, abdomen, and pelvis [o]	x		x [p]	x [p]	x [p]	x	
PET scan or bone scan [o]	x [n]			x [q]			
Head CT or MRI scan [o]	x [r]			x [s]			
Treatment							
Erlotinib (all cycles)		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, and ECG should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients who discontinue study treatment regardless of reason for discontinuation will be followed for survival every 3 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of EGFR activating mutation (see Appendix 5) should occur prior to performing other trial-related assessments.

[g] ECG to determine QTc interval measurement.

[h] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[i] Study drug compliance will be reviewed with the patient.

[j] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[k] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed $\leq$7 days prior to first dose of trial treatment.

[l] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[m] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[n] Only if clinically indicated.

[o] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[p] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[q] Only if abnormal at baseline and if necessary to determine response to treatment.

[r] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[s] Only if abnormal at baseline.

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers

(Enrollment to Treatment Arm Closed to Enrollment)

Treatment of patients with solid tumors that harbor BRAF mutations is part of the clinical trial outlined in the main protocol. This appendix contains details and study requirements that are specific to treatment with vemurafenib plus cobimetinib, including:

A8-4 MATERIALS AND METHODS

A8-4.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol. Listed here are additional requirements specific to treatment with vemurafenib plus cobimetinib.

A8-4.1.1 Additional Inclusion Criteria

- BRAF mutation positivity as determined by next generation sequencing (NGS) or real time-polymerase chain reaction (RT-PCR) as determined in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory will be accepted.
  - Standard assays using polymerase chain reaction (PCR)- or next generation sequencing (NGS)-based technologies for DNA derived from formalin-fixed paraffin-embedded human tumor tissue or in circulating tumor DNA derived from blood samples, which identify the presence of BRAF V600 mutations will be allowed.
  - For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
  - For information regarding specific testing methodologies and allowable identified mutations, see Appendix 5.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of <1%

per year during the treatment period and for at least 6 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

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

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

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

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

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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.

A8-4.1.2 Additional Exclusion Criteria

- Malignant melanoma, papillary thyroid cancer, colorectal cancer, or hematologic malignancy including multiple myeloma
- Left ventricular ejection fraction (LVEF) below institutional lower level of normal (LLN) or below 50%, whichever is lower
- History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration
  - Patients will be excluded from study participation if they are known to have any of the following risks factors for RVO:
    - History of serous retinopathy
    - History of retinal vein occlusion
    - Evidence of ongoing serous retinopathy or RVO at baseline
- Presence of any of the following conditions, which are risk factors for RVO:
  - Uncontrolled glaucoma with intraocular pressure > 21 mm Hg

  - Serum cholesterol ≥Grade 2
  - Hypertriglyceridemia ≥Grade 2
  - Hyperglycemia (fasting) ≥Grade 2
  - Grade ≥2 uncontrolled hypertension (patients with a history of hypertension controlled with anti-hypertensive medication to Grade ≤1 are eligible)
- Prior or concurrent malignancy with known RAS mutation
- Previous treatment with vemurafenib or any other BRAF inhibitor (prior sorafenib is allowed)
- Previous treatment with cobimetinib or any other MEK inhibitor
- Prior treatment with a RAF inhibitor
- Inability to swallow pills
- Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude absorption of vemurafenib
- History of congenital long QT syndrome or mean (average of triplicate measurements) corrected QT (QTc) measured using Fridericia's method ≥450 ms at baseline or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus)

A8-4.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (Section 4.2).

A8-4.3 STUDY TREATMENT

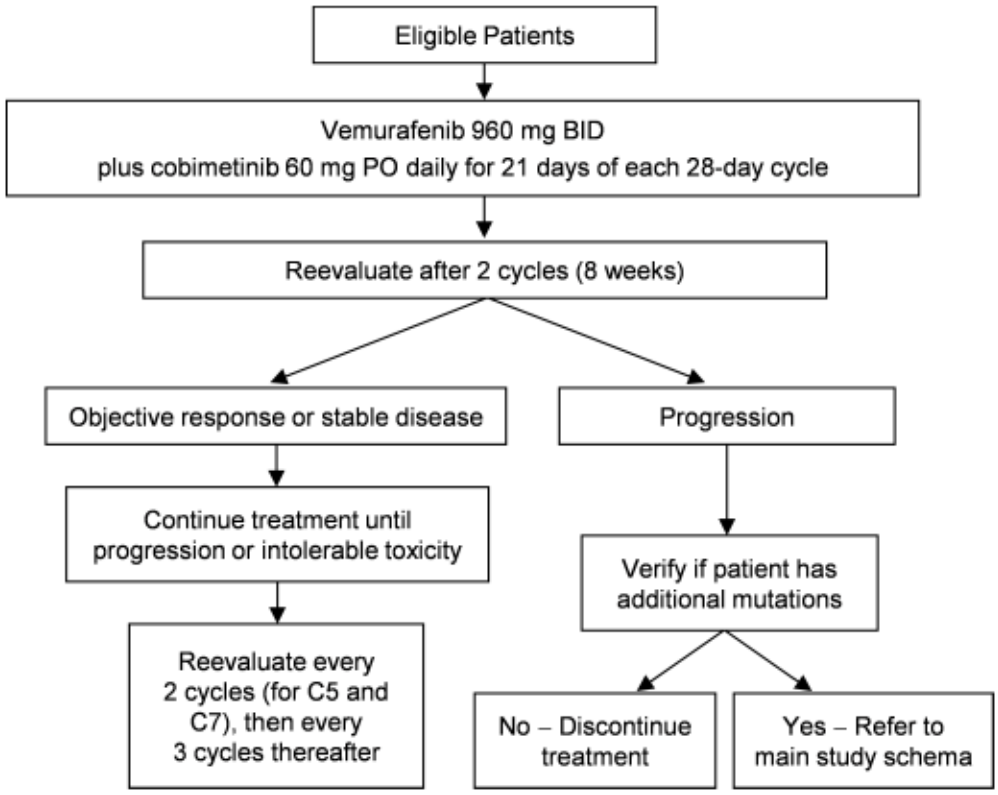
All patients will receive treatment with vemurafenib given by a twice-daily (BID) oral (PO) plus cobimetinib PO daily for 21 days on and 7 days off of each 28-day cycle (21/7; schedule in cycles of 28 days/4 weeks' duration). A schema of the study design is presented in A8-Figure 1.

All patients will receive:

- Vemurafenib 960 mg PO BID
- Cobimetinib 60 mg PO daily for 21 days on and 7 days off of each 28-day cycle (21/7)
- No routine premedications or concomitant medications are required.
  - Patients with BRAF alterations that are already enrolled and receiving vemurafenib will not have cobimetinib added to their study treatment.
  - Refer to the vemurafenib dose modification schedule (A8-Table 1) and the vemurafenib plus cobimetinib dose modification schedule (A8-Table 2) for management of adverse events.

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

A8-Figure 1: Study Schema: Vemurafenib plus Cobimetinib



C=cycle.

A8-4.3.1 Vemurafenib (Zelboraf®)

Vemurafenib is a low molecular weight, orally available inhibitor of the activated form of the BRAF serine-threonine kinase enzyme, which is commonly found in melanoma. Vemurafenib selectively inhibits oncogenic BRAF kinase.

a. Formulation

The formulated drug product vemurafenib is provided in 240-mg film-coated tablets and packed in bottles for administration.

b. Dosage, Administration, and Storage

The two daily doses of vemurafenib should be taken approximately 12 hours apart, with or without a meal. Tablets should be swallowed whole with a glass of water. Tablets should not be chewed or crushed. If a dose is missed, it can be taken up to 4 hours prior to the next dose to maintain the twice daily regimen. Both doses should not be taken at the same time. Vemurafenib should not be taken with grapefruit or grapefruit juice. If vomiting occurs after taking vemurafenib, the patient should be instructed **not** to retake the dose. Patients should take the next scheduled dose of medication. If vomiting persists, the patient should contact the study doctor.

Storage

Vemurafenib tablets should be stored at room temperature, between 15°C and 25°C and should be protected from excessive exposure to sunlight.

c. Risks Associated with Vemurafenib

The toxicity profile for vemurafenib has been documented from safety data derived from seven studies of over 6,000 treated patients with locally advanced unresectable or metastatic melanoma. The most common toxicities observed were rash, fatigue, arthralgia, myalgia, headache, nausea, photosensitivity, alopecia, and pruritus. The most common laboratory abnormalities reported as adverse events included elevations of liver function tests (i.e., γ glutamyltransferase, alkaline phosphatase, ALT, AST, and bilirubin).

The majority of adverse events reported in conjunction with Phase I through III clinical trials were of mild or moderate severity. Approximately one-half of all patients treated with vemurafenib required interruption and/or reduction of dose on at least one occasion although treatment discontinuation due to adverse events has been rare.

Approximately 20% of vemurafenib recipients developed one or more localized cutaneous squamous cell carcinomas (mainly keratoacanthoma type). The majority of these were observed within the first 16 weeks of vemurafenib exposure and were not treatment limiting. Cases of cutaneous squamous cell carcinoma were typically managed with simple excision, and patients generally continued on treatment without dose modification.

Analysis of ECG data from the Phase II, NP22657 study of vemurafenib in metastatic melanoma patients (Genentech, data on file) revealed a risk of QT interval prolongation without associated clinical symptomatology.

Two cases of squamous cell carcinoma of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled on a clinical trial. In addition, two cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for >2 years.

On the basis of its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. In addition, progression of pre-existing RAS-mutant malignancies (chronic myelomonocytic leukemia, pancreatic cancer) have been reported in patients treated with vemurafenib. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation. Mild to severe skin photosensitivity has been reported in patients treated with vemurafenib. All patients should be advised to minimize sun exposure, wear protective clothing, and use a broad-spectrum ultraviolet A/ultraviolet B sunscreen and lip balm (SPF ≥30), reapplied

every 2 to 3 hours, when outdoors during vemurafenib treatment and for at least 5–10 days after discontinuing vemurafenib.

Pancreatitis has also been identified as a risk with vemurafenib use. The Sponsor recommends that serum amylase and lipase testing be conducted as part of the workup of any suspected case of pancreatitis in addition to other appropriate testing (e.g., computed tomography of the abdomen).

An assessment of liver-related adverse events reported with vemurafenib use showed that 63 cases of medically confirmed serious adverse events were drug-induced liver injury (DILI) on the basis of clinical chemistry criteria from the DILI Expert Working Group (Aithal et al. 2011). Of the 63 cases, two were assessed as severe; both were reported as hepatic failure. The outcome of both cases of hepatic failure have been reported to be completely resolved following vemurafenib discontinuation. There were no reported deaths among the 63 cases of liver injury. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to alkaline phosphatase ratio was 1.5, suggesting a trend toward cholestatic pattern of liver injury. There were no risk factors or populations at risk identified.

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase II QT substudy in patients with metastatic melanoma. QT prolongation may lead to an increased risk of ventricular arrhythmias, including torsades de pointes. Patients with a history of congenital long QT syndrome, QTc interval corrected using Fridericia's method ≥ 450 ms, or uncorrectable abnormalities in serum electrolytes will be excluded from study. ECG and electrolytes, including potassium, magnesium, and calcium, will be monitored throughout the study. In addition, investigators should closely monitor patients who are on medications or supplements that may affect the QT interval. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their randomization in this study.

An adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. This is based on twenty cases of radiation injuries, adjudicated as radiation recall (n=8) and radiation sensitization (n=12). The nature and severity of the events in all 20 cases were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation with fatal outcome in 3 cases. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Full details are provided in the Vemurafenib IB.

An adverse drug reaction of acute kidney injury, including interstitial nephritis following vemurafenib administration, has been identified in patients being treated with vemurafenib. The majority of these cases were characterized by mild to moderate

increases in serum creatinine (some observed in the setting of dehydration events) with recovery after dose modification. Approximately 2% of acute kidney injury cases were biopsy–proven interstitial nephritis, and approximately 3% of acute kidney injury cases were acute tubular injury/necrosis. No fatal cases were related to acute kidney injury.

Renal function should be monitored in patients undergoing vemurafenib treatment. Vemurafenib dose modification guidelines should be utilized when applicable, and it is recommended to routinely monitor serum creatinine levels in all patients undergoing vemurafenib therapy.

Dupuytren's contracture and plantar fascial fibromatosis have been reported with vemurafenib. The majority of cases were mild to moderate, but severe, disabling cases of Dupuytren's contracture have also been reported.

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with vemurafenib and upon re-initiation of treatment. Severe hypersensitivity reactions included generalized rash and erythema or hypotension. Drug reaction with eosinophilia and systemic symptoms has been reported in association with vemurafenib in the postmarketing setting. Severe dermatologic reactions have been reported in patients receiving vemurafenib, including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Serious ophthalmologic reactions, including uveitis, have been reported in patients treated with vemurafenib. Retinal vein occlusion has been observed and is a potential risk.

Cases of VIIth nerve paralysis have been observed in patients treated with vemurafenib. In clinical trials, these events resolved without sequelae. Neutropenia has been identified as an uncommon adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6–12 weeks of treatment. It appears to be reversible usually within 2 weeks, with temporary interruption, dose reduction, or discontinuation of vemurafenib, and in some cases has been managed with granulocyte colony-stimulating factor.

d. Dosage Modification

For management of specific toxicities and dose modification guidelines, see A8-Table 1 (vemurafenib only) and A8-Table 2 (vemurafenib plus cobimetinib).

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

A8-Table 1: Dose Modification for Vemurafenib

CTCAE Grade	Action
Grade 1–2 (tolerable)	Maintain dose at 960 mg BID
Grade 2 (intolerable) or Grade 3	
1st Appearance	Interrupt until Grade 0–1. Resume dosing at 720 mg BID.
2nd Appearance	Interrupt until Grade 0–1. Resume dosing at 480 mg BID.
3rd Appearance	Discontinue permanently.
Grade 4	
1st Appearance	Discontinue permanently or interrupt vemurafenib until Grade 0–1. Resume dosing at 480 mg BID.
2nd Appearance	Discontinue permanently.

BID=twice daily; CTCAE = Common Terminology Criteria for Adverse Events.

A8-4.3.2 Cobimetinib (Cotellic®)

Cobimetinib is a reversible inhibitor of MEK1 and MEK2. MEK proteins are upstream regulators of the extracellular signal-regulated kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E and V600K mutations result in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2.

a. Formulation

The formulated drug product cobimetinib is provided in 20-mg, film-coated, immediate-release tablets packaged in blister packs.

b. Dosage, Administration, and Storage

The daily dose of cobimetinib should be taken for 21 days on, then 7 days off, in a 28-day treatment cycle. Cobimetinib should be taken once daily, at approximately the same time each day. At least 7 days off cobimetinib is required prior to starting a new treatment cycle.

Cobimetinib can be taken with or without a meal. Cobimetinib tablets should never be chewed, cut, or crushed.

If vomiting occurs after taking cobimetinib, the patient should be instructed NOT to retake the dose. Patients should take the next scheduled dose of medication. If vomiting persists, the patient should contact the study doctor.

Storage

Cobimetinib tablets should be stored below 30°C.

c. Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from the Phase III Study GO28141 (cobimetinib plus vemurafenib), Phase Ib Study NO25395 (cobimetinib plus vemurafenib), and Phase I Study MEK4592g (cobimetinib monotherapy). For further information regarding clinical safety, please refer to the current Cobimetinib Investigator's Brochure.

Important Identified Risks Associated with Cobimetinib

Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III study GO28141, Grade 1–4 hemorrhagic events were reported in 13.0% of patients treated with cobimetinib plus vemurafenib, and in 7.3% of patients treated with placebo plus vemurafenib. The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3–4 hemorrhage events were reported in 1.2% of patients who received cobimetinib plus vemurafenib and 0.8% of patients who received placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients who use concomitant medications that increase the risk of bleeding (including anti-platelet or anticoagulant therapy).

Instructions and dose modification for hemorrhage events are included in A8-Table 2 below.

Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including cobimetinib (Flaherty et al. 2012). Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment, and retinopathy. Serous retinopathy events may also be asymptomatic.

Serous retinopathy has been characterized in the Phase III Study GO28141. The study incorporated prospective serial ophthalmic examinations for all enrolled patients. Serous retinopathy was reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (25.5% vs. 2.8%, respectively), and approximately half the events were asymptomatic Grade 1 events. Few patients treated with cobimetinib plus vemurafenib experienced Grade ≥ 3 ocular events (2.8%); the majority of these were managed with dose modification of both cobimetinib and vemurafenib.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmologic examinations at specified timepoints throughout the study. Details regarding baseline and subsequent ophthalmologic examinations are provided in Sections A8-4.5.2 through A8-4.5.5, and A8-Table 3.

Guidelines for management of patients who develop Grade ≥ 2 visual disorders or retinopathy are provided in A8-Table 2 below.

Left Ventricular Dysfunction

Decrease in left ventricular ejection fraction (LVEF) from baseline has been reported in patients receiving cobimetinib. Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in left ventricular ejection fraction events may be asymptomatic.

Left ventricular dysfunction has been characterized in the Phase III Study GO28141. The study incorporated prospective serial left ventricular ejection fraction evaluation in all patients. With active surveillance, measured reductions in left ventricular ejection fraction were observed more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (26% vs. 19%, respectively, of Grade 2 or 3 decrease). Of the patients treated with cobimetinib plus vemurafenib, 2 patients (0.8%) had symptomatic reduction in left ventricular ejection fraction and the remaining patients were asymptomatic. Most left ventricular ejection fraction reduction events in patients on cobimetinib plus vemurafenib (62%) improved or resolved with management according to the dose-modification guidelines (see A8-Table 2 below).

Rhabdomyolysis and CPK Elevations

Elevations in creatine phosphokinase (CPK) have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported was asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in post-marketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥ 3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for dose modifications for elevated CPK and rhabdomyolysis are included in A8-Table 2 below.

Photosensitivity (when Administered with Vemurafenib)

No evidence of phototoxicity has been observed with cobimetinib as a single agent. However, photosensitivity was observed on Study GO28141 with a higher frequency in the cobimetinib plus vemurafenib arm versus the placebo plus vemurafenib arm (46% vs. 35%, respectively). The majority of events were Grades 1 or 2, with Grade ≥ 3 events occurring in 4% of patients in the cobimetinib plus vemurafenib arm versus 0% in the placebo plus vemurafenib arm. Grade 3 photosensitivity events in the cobimetinib plus vemurafenib arm were treated with primary topical medication in conjunction with interruption of study agents. Refer to A8-Table 2 below for photosensitivity management guidelines.

Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered non-serious and of low-severity grade. In the Phase III study GO28141, pneumonitis events were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (1.6% vs. 0.4%, all grades). There were no reported Grade ≥3 events in either study arm. Serious events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib.

Potential Risks Associated with Cobimetinib
Liver Laboratory Abnormalities and Severe Hepatotoxicity

Liver laboratory test abnormalities, including increases in ALT, AST, and alkaline phosphatase, have been reported as adverse events and serious adverse events in patients treated with cobimetinib plus vemurafenib.

In the Phase III Study GO28141, liver laboratory test abnormalities reported as Grade ≥3 adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (20.5% vs. 15.1%, respectively):

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms, the majority of Grade ≥3 liver laboratory test abnormalities resolved.

Instructions and dose modification for liver function test elevations are included in A8-Table 2.

Impaired Female Fertility

There is a potential for effects on fertility and embryo-fetal toxicity based on results from nonclinical studies.

While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. These changes were reversible upon discontinuation of cobimetinib administration.

Teratogenicity and Development Toxicity

There are no data regarding the use of cobimetinib in pregnant women. In a dedicated nonclinical embryo-fetal toxicity study, cobimetinib produced fetal toxicity (resorptions and reductions in fetal weight), and teratogenicity (malformations of the great vessels and skull) at similar systemic exposures in rat to those observed in patients administered the 60 mg dose. Therefore, teratogenicity and developmental toxicity is a potential risk for cobimetinib, and cobimetinib use is not recommended during pregnancy.

Other Risks Associated with Cobimetinib

Rash

In the Phase III study GO28141, combined rash events of all types and grades were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (71.7% vs. 66.7%, respectively), although Grade ≥3 events (approximately 16% of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (39% all grades, 5.9% Grade ≥3, 1.6% serious adverse events) and rash maculo-papular (14.6% all grades, 6.3% Grade ≥3, 1.2% serious adverse events).

Generally, Grade ≥3 rash events were effectively managed with dose modification guidelines. In GO28141, approximately 90% of Grade ≥3 rash events resolved in both arms.

Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult cancer patients.

In the Phase III study GO28141, diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in 59.9% of patients and Grade 3 or 4 events were reported in 6.5% of patients treated with cobimetinib plus vemurafenib versus 30.9% and 0.8%, respectively, in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported in 1.2% of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III study GO28141, nausea and vomiting events were reported more frequently in

the active cobimetinib arm than the control arm (nausea 39.0% vs. 23.8%; vomiting 21.3% vs. 12.1%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea 0.8%, vomiting 1.2%).

In the Phase I single-agent study (MEK4592g), all grades of nausea and vomiting were both reported as 33.9% with 0.9% reported for Grade ≥3 nausea and none reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine antiemetic prophylaxis is not recommended.

Hypersensitivity

There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to cobimetinib monotherapy or cobimetinib when used with other agents. These have appeared to be isolated reports, and in some cases, occurred in patients with histories of drug allergies. Thus, the relationship of cobimetinib to these events is unclear.

In the Phase III Study GO28141, Grade 3 hypersensitivity events were reported in 3 patients in the cobimetinib and vemurafenib arm compared with no such events in the placebo plus vemurafenib arm. All events required hospitalization and treatment with steroids.

Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction.

Please refer to the Cobimetinib Investigator's Brochure for additional safety information.

d. Dose Modifications

For management of specific toxicities and dose modification guidelines, see A8-Table 2 below.

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

A8-Table 2: Management of Specific Toxicities and Dose Modification Guidelines

Adverse Event	Action
A) Rash Grade ≥3	The appearance of rash must be characterized as acneiform or non-acneiform. No change in vemurafenib and cobimetinib dosing will be implemented for Grade ≤2 rash; patients should receive maximal supportive care per institutional guidelines. Acneiform rash Hold cobimetinib dosing until Grade ≤2. Vemurafenib dosing may continue when cobimetinib is interrupted. Reduce cobimetinib by 1 dose level. If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥3, further reduce cobimetinib by another dose level. Permanently discontinue cobimetinib if restarting after second dose reduction, the patient experiences skin toxicity Grade ≥3. Permanently discontinue cobimetinib if rash ≥ 3 persists for > 28 days despite adequate supportive care. Non-acneiform or maculo-papular rash Delay vemurafenib dosing until Grade ≤2. Cobimetinib dosing may continue when vemurafenib is interrupted. For Grade 3 rash, reduce vemurafenib by 1 dose level. If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥3, further reduce vemurafenib by 1 dose level. Permanently discontinue vemurafenib if restarting after second dose reduction, the patient experiences recurrent skin toxicity Grade ≥3. For Grade 4 rash, reduce vemurafenib by 2 dose levels. Permanently discontinue vemurafenib if after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3.

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

Adverse Event	Action
B) Photosensitivity Grade ≥ 3	a) Grade ≤ 2 photosensitivity should be managed with supportive care and treatment of both vemurafenib and cobimetinib may be continued. If Grade 2 photosensitivity does not resolve to Grade ≤ 1 after 7 days or if photosensitivity worsens to Grade ≥ 3 despite best supportive care, then both vemurafenib and cobimetinib treatment must be interrupted until the photosensitivity resolves to a Grade ≤ 1. b) If resolution to Grade ≤ 1 occurs within 28 days, treatment may be re-initiated with vemurafenib dose reduced by 1 level and without change in cobimetinib dose. If the photosensitivity does not resolve to Grade ≤ 1 by 28 days, then the therapy with vemurafenib and cobimetinib should be discontinued. c) If the photosensitivity recurs to Grade ≥ 3 with vemurafenib and cobimetinib, re-initiation despite prophylactic measures and dose reduction of vemurafenib, then both agents should be held until the photosensitivity resolves to Grade ≤ 1 or less. The dose of vemurafenib should be reduced by another dose level. d) If photosensitivity recurs a second time to Grade ≥ 3 despite prophylactic measures and the aforementioned 2 dose reductions of vemurafenib, vemurafenib should be discontinued. The patient may continue on study treatment with cobimetinib/placebo alone.
C) New skin lesion, suggestive of any cutaneous primary malignancy. Any cutaneous primary malignancy is considered a Grade 3 event in this study.	a) Interrupt vemurafenib and cobimetinib for 48 hours before and after excisional biopsy. This period of interruption may be altered based upon experience in this study. b) If lesion is diagnosed as cuSCC, treatment may be re-instituted with vemurafenib and cobimetinib at pre-event dose levels after the lesion is excised. If the lesion is not excised, vemurafenib treatment must be discontinued. c) If the lesion is not an SCC, then treatment with vemurafenib and cobimetinib may be restarted at the most recent dose level. Cases of cutaneous squamous cell carcinoma were typically managed with simple excision, and patients generally continued on treatment without dose modification.

<table>
<tr><th>Adverse Event</th><th>Action</th></tr>
<tr><td>D) Visual symptoms ≥Grade 2</td><td>NCI CTCAE v4.0 Eye Disorders – Other, specify:
<table>
<tr><th>Grade</th><th>Description</th></tr>
<tr><td>1</td><td>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td></tr>
<tr><td>2</td><td>Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL</td></tr>
<tr><td>3</td><td>Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL</td></tr>
<tr><td>4</td><td>Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye</td></tr>
</table>
Interrupt cobimetinib and vemurafenib.
Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography
If retinal vein occlusion (RVO) is diagnosed, vemurafenib and cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines.
If neurosensory retinal detachment is diagnosed, cobimetinib dosing should be interrupted until symptoms improve to Grade 1. Then cobimetinib should be dose reduced by 1 dose level when restarting. If visual symptoms of Grade≥2 recur despite 2 dose level reductions of cobimetinib, cobimetinib should be permanently discontinued. The patient may continue on study treatment with vemurafenib alone in the event that cobimetinib/placebo is discontinued.
If uveitis/iritis is diagnosed, Grade ≤2 uveitis/iritis can be managed with ophthalmologic input using local non-invasive therapies and/or short courses of systemic therapy. Dose reduction of study drugs is NOT required if uveitis/iritis is Grade ≤2. For Grade ≥3 uveitis/iritis, vemurafenib should be reduced by 1 dose level.
If RVO, neurosensory retinal detachment or uveitis/iritis are NOT identified:
• and visual symptoms have not resolved to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, permanent discontinuation of both study drugs should be considered.
• and visual symptoms have resolved to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, resume use of vemurafenib and cobimetinib at current doses.
• If visual symptoms of Grade ≥2 (despite the optimal use of local / non-invasive supportive care) recur, vemurafenib and/or cobimetinib should be dose reduced by 1 level, depending on which agent is implicated. If visual symptoms of Grade ≥2 recurs despite 2 dose level reductions of both vemurafenib and cobimetinib, and maximal supportive care, vemurafenib and cobimetinib should be permanently discontinued.</td></tr>
</table>

Adverse Event	Action
E) Diarrhea Grade >3	a) No change in vemurafenib and cobimetinib dosing will be implemented for Grade ≤2 diarrhea; patients should receive maximal supportive care. b) If Grade ≥3 diarrhea occurs despite adequate supportive care, then both drugs should be held until the diarrhea has improved to Grade ≤1. • If this occurs within 28 days, vemurafenib and cobimetinib may be restarted with cobimetinib reduced by 1 dose level, with continued supportive care or prophylaxis. • If bowel movement characteristics have NOT improved to Grade ≤1 or baseline with maximal supportive care by 28 days, then both drugs should be discontinued. d) If Grade ≥3 diarrhea recurs despite supportive care and cobimetinib dose reduction, vemurafenib and cobimetinib should be held until the diarrhea resolves to Grade ≤1. If this occurs within 28 days, then therapy may be re-initiated with vemurafenib reduced by 1 dose level. The cobimetinib dose will be maintained at the previously reduced dose. e) If the diarrhea recurs at Grade ≥3 despite supportive care and dose reductions of 2 dose levels in both drugs (i.e., vemurafenib to 480 mg BID and cobimetinib to 20 mg QD), then both drugs should be permanently discontinued.

Adverse Event	Action
F) Rhabdomyolysis or CPK elevations	Rhabdomyolysis or symptomatic CPK elevations: Interrupt cobimetinib treatment. If severity is improved by at least on grade within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when cobimetinib treatment is modified, if clinically indicated. If rhabdomyolysis or symptomatic CPK elevation do not improve within 4 weeks, permanently discontinue cobimetinib treatment. Asymptomatic CPK elevations: Grade ≤3: cobimetinib dosing does not need to modified or interrupted to manage asymptomatic Grade ≤3 CPK elevations. Grade 4: Interrupt cobimetinib treatment. If improved to Grade ≤3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when cobimetinib treatment is modified, if clinically indicated. If CPK elevations do not improve to Grade ≤3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment.

<table>
<tr><th>Adverse Event</th><th>Action</th></tr>
<tr><td>G) LFT elevations</td><td>a) If Grade ≤2, continue current dose of vemurafenib and cobimetinib.
b) If Grade 3, hold vemurafenib. Continue current dose of cobimetinib. Upon resolution of LFT to Grade ≤1, resume vemurafenib at 1 lower dose level (e.g., 960 mg to 720 mg, or 720 mg to 480 mg).
c) If Grade 4, see Section J below.
d) No dose modification is required for isolated GGT elevation in the absence of clinically significant elevation above baseline grade in AST, ALT, ALP, bilirubin or hepatic.</td></tr>
<tr><td>H) QTcF interval prolongation on ECG Grade ≥ 3</td><td>a) Rule out other risk factors for arrhythmia (e.g., myocardial ischemia); check for electrolyte disturbances (particularly potassium and magnesium levels) in all cases.
b) Evaluate concomitant medications to determine if there is co-administration of drugs that prolongs QTc interval in all cases (e.g., 5-HT_3 receptor antagonist anti-emetics).
c) Interrupt dosing of vemurafenib ECG monitoring should be performed until QTc interval decreases below 500 ms. Electrolytes abnormalities should be corrected in all cases. Continue dosing with cobimetinib at the current dose if otherwise tolerated.
d) Plan to seek a cardiologist consultation or advice.
e) If QTc interval does not improve within 28 days after interruption of vemurafenib dosing, permanently discontinue vemurafenib; continue dosing with cobimetinib at the current dose.
f) If QTc improves within 28 days, restart dosing of vemurafenib at 1 reduced dose level.
g) Repeat 12-lead ECG monitoring at 2 weeks and 4 weeks of restarting vemurafenib at the lower dose. Additional ECG monitoring will be performed at Day 15 of each subsequent Cycle for 3 cycles, and every 3 months thereafter.
h) If second increase in QTc interval to >500 ms occurs at the lower dose of vemurafenib, follow guidelines above, and reduce dose of vemurafenib by an additional dose level.
i) Permanently discontinue vemurafenib if after correction of associated risk factors and dose reductions, the QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values.</td></tr>
<tr><td>I) Reduction in LVEF</td><td>NCI CTCAE v 4.0 EF decreased:
<table>
<tr><th>Grade</th><th>Description</th></tr>
<tr><td>1</td><td>-</td></tr>
<tr><td>2</td><td>Resting EF 50%–40%;
10%–19% drop from baseline</td></tr>
<tr><td>3</td><td>Resting EF 39%–20%;
>20% drop from baseline</td></tr>
<tr><td>4</td><td>Resting EF <20%</td></tr>
</table>
a) Asymptomatic decrease in LVEF</td></tr>
</table>

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

Adverse Event	Action
	See A8-Table 3 All patients who require dose reduction of cobimetinib should have LVEF measurements at 2 weeks, 4 weeks, then every 6 weeks for 12 weeks, and then per protocol. b) Symptomatic decrease in LVEF or symptomatic heart failure Cardiology consultation is strongly recommended. Hold cobimetinib. Vemurafenib may be continued. Strong consideration should be given to permanently discontinuing cobimetinib if it is attributed to have caused the cardiac symptoms. If cardiac symptoms resolve completely within 28 days, and LVEF returns to LLN, reduce cobimetinib by 1 dose level. The patient should have LVEF measurements at 2 weeks, 4 weeks, then every 6 weeks for 12 weeks, and then per protocol. If cardiac symptoms resolve within 28 days, but LVEF is below LLN, see A8-Table 3. If cobimetinib is permanently discontinued, patient may continue on vemurafenib.
J) Other Grade 4, non–hematologic adverse events related to study drug (except for GGT or CPK elevation)	a) Interrupt dosing of vemurafenib and cobimetinib. b) If adverse event resolves to Grade ≤1 within 28 days, then restart dosing of vemurafenib and cobimetinib. Vemurafenib should be decreased by 2 dose levels and cobimetinib by 1 dose level. c) If the adverse event does not resolve to Grade ≤1 by 28 days, discontinue study treatment. d) If the Grade 4 adverse event recurs (a second time), then both agents should be discontinued.
K) Hemorrhage	Grade 3 events: Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. Vemurafenib dosing can be continued when cobimetinib treatment is interrupted, if clinically indicated. Grade 4 events or cerebral hemorrhage (all grades): Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib.

ADL=activities of daily living; ALK=anaplastic lymphoma kinase; ALP=alkaline phosphatase; BID=twice daily; CPK=creatine phosphokinase; cuSCC=cutaneous squamous cell carcinoma; EF=ejection fraction; GGT=γ glutamyltransferase; LFT=liver function test; LLN=lower limit of normal; LVEF=left ventricular ejection fraction; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; QD=once daily; QTc=corrected QT interval; RVO=retinal vein occlusion; SCC=squamous cell carcinoma.

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

A8-Table 3 Recommended Dose Modifications for Cobimetinib in Patients with Left Ventricular Ejection Fraction Decrease from Baseline

Left Ventricular Ejection Fraction (LVEF) Decrease from Baseline			
LVEF value	**Recommended action with cobimetinib**	**LVEF value following treatment break**	**Recommended cobimetinib daily dose [a]**
Asymptomatic Patient			
≥ 50% (or 40%–49% and < 10% absolute decrease from BL)	Continue at current dose	N/A	60 mg
< 40% (or 40%–49% and ≥ 10% absolute decrease from BL)	Interrupt treatment for 2 weeks	< 10% absolute decrease from BL	First occurrence: 40 mg
			Second occurrence: 20 mg
			Third occurrence: permanent discontinuation
		< 40% (or ≥ 10% absolute decrease from BL)	Permanent discontinuation
Symptomatic Patient			
N/A	Interrupt cobimetinib treatment.[b]	Asymptomatic and < 10% absolute decrease from BL	First occurrence: 40 mg
			Second occurrence: 20 mg
			Third occurrence: Permanent discontinuation
		Asymptomatic and < 40% (or ≥ 10% absolute decrease from BL)	Permanent discontinuation
		Symptomatic regardless of LVEF	Permanent discontinuation

BL = baseline; LVEF = left ventricular ejection fraction; N/A = not applicable.

[a] For all patients restarting treatment, re-evaluate LVEF at 2, 4, 10, and 16 weeks and then every 12 weeks (X cycles as per protocol) or as clinically indicated until treatment discontinuation.

[b] Consult Medical Monitor for approval to withhold cobimetinib for 4 weeks. Cardiology consultation is strongly recommended.

A8-4.4 CONCOMITANT AND EXCLUDED THERAPIES

A8-4.4.1 Concomitant Therapy

Please refer to the main body of the protocol (Section 4.4.1) for concomitant therapies allowed.

Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.

Pain medications may be administered according to local standard practice guidelines while the patient is in the study.

Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the course of the study.

A8-4.4.2 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.
- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial.
- Concomitant treatment with drugs that are strong inducers or inhibitors of the CYP3A4 enzymes should be avoided if possible. If possible, patients who are taking such agents should be switched to other agents that do not share CYP3A4 inhibition/induction.
- Vemurafenib may increase plasma exposure of drugs primarily metabolized by CYP1A2. Dose adjustment for medications metabolized by CYP1A2 should be considered.
- Palliative radiotherapy or major surgery within 14 days prior to first dose of study treatment is prohibited.

A8-4.4.3 Prohibited Foods and Supplements

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment, unless otherwise specified below:

- St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
- Grapefruit juice (potent CYP3A4 enzyme inhibitor)

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever comes first. These patients will also continue to be followed for survival.

A8-4.5 STUDY ASSESSMENTS

All patients should visit the study center on the days specified in A8-Table 2 of this appendix. Molecular profiling reports must be seen and reviewed by the investigator prior to proceeding with other study-specific assessments. The complete schedule of assessments for patients receiving vemurafenib plus cobimetinib is contained in the study flowchart of this appendix. Baseline medical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), complete blood counts (CBC), comprehensive metabolic profile (CMP), creatine phosphokinase (CPK), and electrocardiogram (ECG) should be done ≤21 days prior to initiation of treatment. If the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1, they do not have to be repeated on Day 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans, LVEF by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan, ophthalmologic examination, and tumor markers to document measurement of disease must be performed ≤4 weeks prior to initiation of treatment.

A8-4.5.1 Descriptions of Study Assessments

Please refer to the main body of the protocol (Section 4.5.1) for details.

A8-4.5.2 Screening and Pretreatment Assessments

- Written informed consent form prior to any trial-related procedures
- Review of molecular profiling report and confirmation of BRAF mutation (should occur prior to obtaining other study-specific assessments). For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- Dermatologic examination for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- Ophthalmologic examination including visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy and spectral domain optical coherence tomography (spectral domain optical coherence tomography [OCT], if not available, may be substituted with time domain OCT) to evaluate evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO, or neovascular macular degeneration
  - Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Ophthalmologic examination should be performed by a qualified ophthalmologist.

- Head and neck examination for squamous carcinomas
- ECOG Performance Status
- ECG, QTc interval measurement
- LVEF assessment with ECHO or MUGA
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with a history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

A8-4.5.3 Assessments during Treatment

Patients will visit the study center once every 4 weeks (±72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 3, Day 1, subsequent visits will be every 12 weeks with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1

- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3

- Dermatologic exam for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- ECG, QTc interval measurement
- AE evaluations

  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK

c. Day 1 of Cycle 2 and Every Three Cycles Thereafter

- LVEF assessment with ECHO or MUGA
- Ophthalmologic examination

d. Day 1 of Cycle 3

- Plasma biomarker collection

e. Day 1 of Cycles 3 and 5

- Head and neck examination for developing squamous carcinomas
- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)

f. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- Dermatologic examination for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- Head and neck examination for developing squamous carcinomas
- ECG, QTc interval measurement
- AE evaluations
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

A8-4.5.4 End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of combination vemurafenib plus cobimetinib. The following assessments will be conducted at the follow-up visit:

- Plasma biomarker collection
- Dermatologic exam for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK
- LVEF assessment with ECHO or MUGA
- Ophthalmologic evaluation
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

A8-4.5.5 Discontinuation of Cobimetinib

Safety follow-up within 30 days of cobimetinib discontinuation should include the following:

- LVEF assessment with ECHO or MUGA
- Ophthalmologic evaluation

CPK, LVEF, and the ophthalmologic evaluation do not need to be repeated when vemurafenib is subsequently discontinued.

A8-4.6 PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

A8-4.7 PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST

Please refer to Section 5.2.3 in the main body of the protocol for protocol-defined adverse events of special interest.

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

A8-Table 4:Vemurafenib plus Cobimetinib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			
			Reassessments		
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)	End-of-Treatment Safety Follow-Up [b]
Tests and Observations					
Informed consent [c]	x				
Obtain/review molecular profiling report/pathology report [d]	x				
Medical history	x				
Dermatologic exam [e]	x	x		x	x
Head/neck exam [f]	x		x	x	
ECOG PS	x				
ECG, QTc interval measurement [g]	x	x		x	
LVEF with ECHO or MUGA	x	x [Day 1 of Cycle 2 & every 3 cycles thereafter]			x [and at discontinuation of cobimetinib [h]]
Ophthalmologic exam	x	x [Day 1 of Cycle 2 & every 3 cycles thereafter]			x [and at discontinuation of cobimetinib [h]]
Adverse event evaluation (all cycles) [i]		x	x	x	x
Study drug compliance review [j]		x	x	x	x

Appendix 8
Vemurafenib plus Cobimetinib in Patients with BRAF-Mutated Cancers (cont.)

Assessments	Pre-Treatment	Trial Treatment			
			Reassessments		
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)	End-of-Treatment Safety Follow-Up [b]
Laboratory Evaluations					
CBC, 3-part differential, and platelets	x	x		x	x
CMP [k]	x	x		x	x
CPK	x	x		x	x [and at discontinuation of cobimetinib [k]]
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x
Pregnancy test [l]	x				
Optional molecular profiling results [m]		x			
Optional archival tumor sample	x [n]				
Staging					
Tumor markers [o]	x		x	x	x
CT scan of chest, abdomen, pelvis [p]	x		x [q]	x [q]	x [q]
PET scan or bone scan [p]	x [o]			x [r]	
Head CT or MRI scan [p]	x [s]			x [t]	
Treatment					
Vemurafenib plus cobimetinib (all cycles) [u]		x	x	x	

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, CPK, and ECG should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment. ECHO/MUGA for LVEF assessment should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Informed consent must be obtained prior to performing any trial-related screening assessments.

[d] Confirmation of BRAF gene alteration (see Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[e] Full dermatologic examination for squamous carcinoma/other suspicious lesions, including, if per standard practice, an examination of the anal and pelvic areas. Lesions suspicious for squamous cell carcinoma should be treated appropriately.

[f] To be performed by the treating physician to monitor for developing squamous cancers.

[g] ECG and electrolytes, including potassium, magnesium, and calcium, should be monitored before treatment with vemurafenib and after dose modification. Monitoring of ECGs should occur on Day 1 of Cycles 1, 2, 3, 7, and every 3 cycles thereafter, or more often as clinically indicated. **Patients with baseline QTc >450 ms are not eligible for this study.** If during treatment the QTc exceeds 500 ms (CTCAE Grade 3), vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms.

[h] To be conducted/collected within 30 days of cobimetinib discontinuation. CPK, LVEF, and the ophthalmologic examination do not need to be repeated when vemurafenib is subsequently discontinued.

[i] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[j] Study drug compliance will be reviewed with the patient.

[k] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[l] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed ≤7 days prior to first dose of trial treatment.

[m] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[n] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[o] Only if clinically indicated.

[p] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[q] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[r] Only if abnormal at baseline and if necessary to determine response to treatment.

[s] Required for patient with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[t] Only if abnormal at baseline.

[u] If cobimetinib is discontinued, treatment with vemurafenib can continue.

Appendix 9
Vismodegib in Patients with Hedgehog Pathway-Mutated Cancers (Activating Mutation of Smoothened or Loss-of-Function Mutation of Protein Patched Homolog-1)

(Treatment Arm Closed to Enrollment)

Treatment of patients with cancers that harbor potentially clinically relevant mutations in the hedgehog pathway (activating mutation of smoothened [SMO] or loss-of-function mutation of protein patched homolog-1 [PTCH-1]) is part of the clinical trial outlined in the main protocol. This appendix contains details and study requirements that are specific to treatment with vismodegib, including:

A9-4 MATERIALS AND METHODS

A9-4.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol. Listed here are additional requirements specific to treatment with vismodegib.

A9-4.1.1 Additional Inclusion Criteria

- Hedgehog-activating mutation positivity as determined by next generation sequencing (NGS) assays performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory will be accepted.
  - Assays using NGS of genes with known or potentially clinically relevant alterations or analysis by real time-polymerase chain reaction (RT-PCR) must identify clinically activating mutations (those with major coding disruptions resulting in an amino acid change that is likely to be detrimental to protein function, including premature stop codons or frameshift mutations early in the coding region).
  - For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
  - For information regarding specific testing methodologies and allowable identified mutations, see Appendix 5.

- All non-hematological adverse events related to any prior chemotherapy, surgery, or radiotherapy must have resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade ≤2 prior to starting therapy.
- Adequate hepatic function assessed by:
  - Total serum bilirubin ≤2.0, unless resulting from hemolysis, Gilbert's syndrome, or liver infiltration with leukemia
  - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 × the upper limit of normal (ULN)
  - Adequate renal function assessed by:
  - Serum creatinine ≤1.5 × ULN
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of <1% per year during the treatment period and for at least 24 months after the last dose of study drug

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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.

A9-4.1.2 Additional Exclusion Criteria

- Basal cell carcinoma of the skin, medulloblastoma, small-cell lung cancer, or hematologic malignancies
- Previous treatment with vismodegib or any other hedgehog pathway inhibitor

- Inability to swallow pills
- Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude absorption of vismodegib

A9-4.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (Section 4.2).

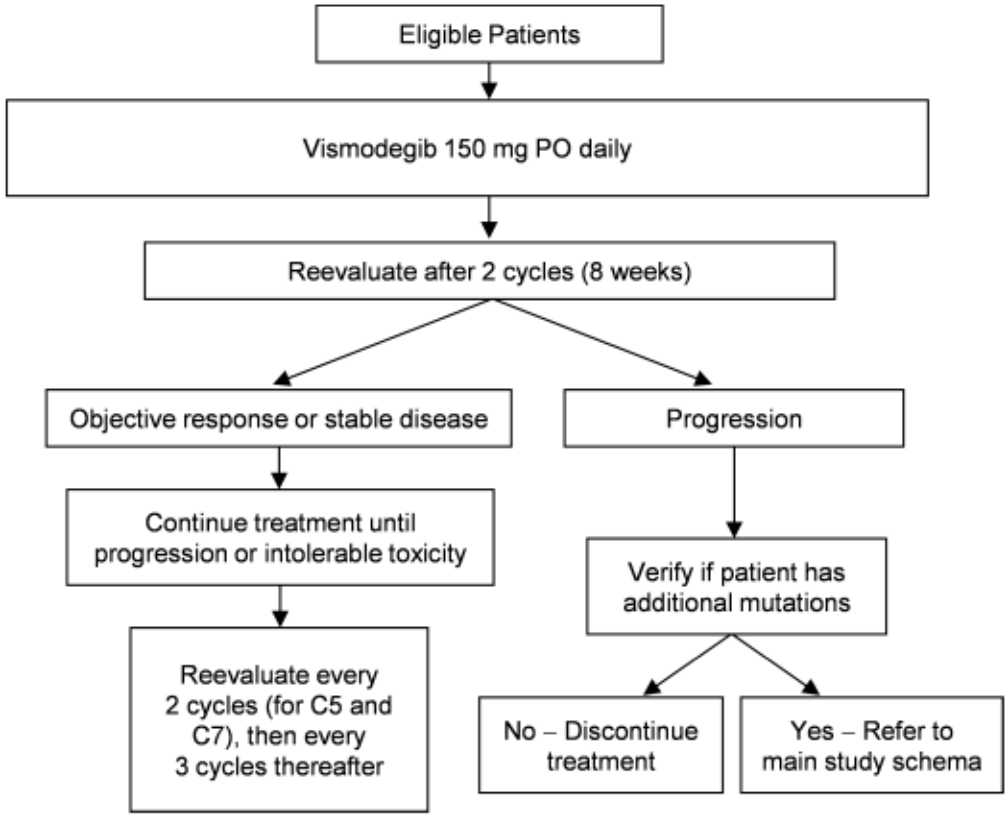
A9-4.3 STUDY TREATMENT

All patients will receive treatment with vismodegib, given at a daily dose of 150 mg orally (PO). Treatment cycles are of 28 days duration. A schematic of the study design is presented in A9-Figure 1 below.

All patients will receive:

- Vismodegib 150 mg PO daily
- No routine premedications or concomitant medications are required.

A9-Figure 1: Study Schema: Vismodegib



C = cycle.

A9-4.3.1 Vismodegib (Erivedge)

Vismodegib is an inhibitor of the hedgehog signaling pathway.

a. Formulation

The formulated drug product vismodegib is provided in 150-mg capsules and has a pink opaque body and a grey opaque cap.

b. Dosage, Administration, and Storage

Vismodegib capsules should be taken at approximately the same time each morning. Each vismodegib dose should be taken with up to 200 mL (approximately 1 cup or 8 oz) of water, and may be taken with or without food. The entire dose must be taken at one time. Vismodegib capsules must be taken whole; they must not be crushed, broken, or dissolved. If a patient inadvertently does not take the vismodegib dose in the morning, he/she may take that day's vismodegib dose any time up to noon that same day. However, if a patient misses taking his/her scheduled vismodegib dose and is unable to take the missed vismodegib dose on the same day, the missed dose will not be "made up." If vomiting occurs after taking vismodegib, the patient should be instructed **not** to retake the dose. Patients should take the next scheduled dose of medication on the following day. If vomiting persists, the patient should contact the study doctor.

c. Dosage Modification

Treatment with vismodegib may be interrupted for up to 4 weeks for evaluation of an intolerable toxicity finding or up to 8 weeks for a planned surgical procedure. In addition, treatment with vismodegib may be interrupted if a patient becomes temporarily unable to swallow capsules. Any other proposed reasons for interruption of treatment should be discussed in advance with the Sarah Cannon Research Institute (SCRI) Development Innovations Medical Monitor.

Intolerable toxicities are defined as new (not present at baseline) Grade 3 or 4 adverse events considered related to vismodegib that are likely to be life-threatening or irreversible, and when in the opinion of the investigator, the risk outweighs the benefit of continued treatment with vismodegib. **The following are not considered intolerable:**

- Grade 3 or 4 events, in the opinion of the investigator, are more likely related to ongoing or recent procedures or concomitant medications other than vismodegib.
- Hematologic or metabolic/chemistry laboratory abnormalities found on routine testing and are not considered clinically significant.
- Musculoskeletal abnormalities, skin ulceration, fracture, debridement or wound care, and dental or periodontal disease related to underlying medical conditions (e.g., basal cell carcinoma)
- Nausea, vomiting, or diarrhea adequately controlled after optimization of medical management

- Grade 3 infection that is transient and treatable or manageable
- Grade 3 sterility

Patients with an asymptomatic or tolerable severe adverse event may continue to receive study drug, provided that the adverse event is manageable and the patient and the investigator agree that continued study participation is acceptable.

If a treatment interruption occurs, and it is determined that vismodegib will be restarted, the original dose will be maintained. There are no planned dose reductions of vismodegib.

If a patient experiences two treatment interruptions, the Medical Monitors must be consulted before the patient can resume treatment.

Given the key role of the hedgehog pathway in embryogenesis and nonclinical data, vismodegib is considered teratogenic; therefore, women who are pregnant or nursing are excluded from this study. WCBP must be counseled on contraception and must be on effective contraception during vismodegib treatment and for at least 24 months after the final dose of vismodegib. Men must use effective contraception during sexual intercourse with female partners while being treated with vismodegib and for at least 3 months after the final dose of vismodegib.

Follow-Up of Pregnancies

Pregnancy is identified as any of the following:

- Pregnancy of a patient actively taking vismodegib or within 24 months after the last dose of vismodegib
- Pregnancy of a female partner of a male patient who is currently taking vismodegib or within 3 months after the last dose of vismodegib

Clinical trial investigators must report pregnancies immediately (within 24 hours) and will be contacted to obtain pregnancy background, pregnancy outcome, pregnancy follow-up, and infant outcome information. Female patients and male patients with pregnant female partners will be contacted to obtain pregnancy information to the extent permitted by local regulations/laws. A Pregnancy Follow-up Form will be sent every trimester or until the pregnancy outcome is known.

Infants born to female patients or female partners of male patients exposed to vismodegib must be followed for 1 year after birth. A Pregnancy Outcome Form for the patient/female partner of a male patient will be sent (when appropriate) within 15 days after expected birth, every quarter until the infant is 1 year old.

Diarrhea

Diarrhea should be treated with standard medications (e.g., loperamide) to avoid dose interruption, if possible.

If Grade 3 or 4 diarrhea develops, treatment should be interrupted, and maximal anti-diarrheal management should be instituted. When diarrhea improves to ≤ Grade 1, vismodegib should be re-introduced at the full dose level, with prophylactic loperamide management.

Nausea/Vomiting

Nausea/vomiting should be managed with standard antiemetic therapy.

d. Vismodegib Warnings and Precautions

The most common adverse reactions (incidence of ≥ 10%) are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, dyspepsia, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia.

Embryo-fetal death and severe birth defects can be caused by vismodegib.

Premature fusion of the epiphyses (EPF) and precocious puberty have been reported in patients exposed to vismodegib. In some cases of EPF, fusion progressed after drug discontinuation.

Amenorrhea has been observed in clinical trials in females of reproductive potential. Reversibility of amenorrhea is unknown.

All patients should be advised not to donate blood or blood products while receiving vismodegib and for at least 24 months after the last dose.

Female patients should not breastfeed while receiving vismodegib and for 24 months after the last dose of vismodegib.

Male patients should be advised not to donate semen while receiving vismodegib and for at least 3 months after the last dose.

A9-4.4 CONCOMITANT AND EXCLUDED THERAPIES

A9-4.4.1 Concomitant Therapy

Please refer to the main body of the protocol (Section 4.4.1) for concomitant therapies allowed.

A9-4.4.2 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.

- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial.

A9-4.5 STUDY ASSESSMENTS

All patients should visit the study center on the days specified in A9-Table 1 of this appendix. Molecular profiling reports must be seen and reviewed by the investigator prior to proceeding with other study-specific assessments. The complete schedule of assessments for patients receiving vismodegib is contained in the study flowchart of this appendix. Baseline medical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), complete blood counts (CBCs), comprehensive metabolic profile (CMP), and serum pregnancy test (for WCBP) should be done ≤ 21 days prior to initiation of treatment. If the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1, they do not have to be repeated on Day 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and tumor markers to document measurement of disease must be performed ≤4 weeks prior to initiation of treatment.

A9-4.5.1 Descriptions of Study Assessments

Please refer to the main body of the protocol for the details of this section.

A9-4.5.2 Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of clinically relevant hedgehog pathway mutations (activating mutations of SMO or loss-of-function mutations of PTCH-1) should occur prior to obtaining other study-specific assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- ECOG performance status
- CBC, including 3-part differential and platelets
- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (only if clinically indicated or patient has a history of treated brain metastases)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

A9-4.5.3 Assessments during Treatment

Patients will visit the study center once every 4 weeks (±72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 3, Day 1, subsequent visits will be every 12 weeks with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1

- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3

- Adverse event (AE) evaluations
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.

c. Day 1 of Cycle 3

- Plasma biomarker collection

d. Day 1 of Cycles 3 and 5

- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)

e. Cycle 4

- Urine or serum pregnancy test: any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.

f. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- AE evaluations
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

A9-4.5.4 End of Treatment

At the end of treatment, a safety follow-up visit will occur within 45 days from discontinuation of vismodegib. The following assessments will be conducted at the follow-up visit:

- Plasma biomarker collection
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.

- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

A9-4.5.5 Follow-Up Assessments

Please refer to the main body of the protocol for the follow-up assessments.

A9-4.6 PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

A9-4.7 PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST (VISMODEGIB)

Please refer to Section 5.2.3 in the main body of the protocol for protocol-defined adverse events of special interest.

Appendix 9
Vismodegib in Patients with Hedgehog Pathway-Mutated Cancers (Activating Mutation of Smoothened or Loss of Function Mutation of Protein Patched Homolog-1) (cont.)
A9-Table 1: Vismodegib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)			
Tests and Observations							
Informed consent [e]	x						
Obtain/review molecular profiling report/pathology report [f]	x						
Medical history	x						
ECOG PS	x						
Adverse event evaluation (all cycles) [g]		x	x	x	x		
Study drug compliance review [h]		x		x	x		
Survival status							x
Laboratory Evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP [i]	x	x		x	x		
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x		
Pregnancy test [j]	x	x	x [and Cycle 4]	x			
Optional molecular profiling results [k]		x					

Appendix 9
Vismodegib in Patients with Hedgehog Pathway-Mutated Cancers (Activating Mutation of Smoothened or Loss of Function Mutation of Protein Patched Homolog-1) (cont.)

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)			
Optional archival tumor sample	x [l]						
Staging							
Tumor markers [m]	x		x	x	x	x	
CT scan of chest, abdomen, pelvis [n]	x		x [o]	x [o]	x [o]	x	
PET scan or bone scan [n]	x [m]			x [p]			
Head CT or MRI scan [n]	x [q]			x [r]			
Treatment							
Vismodegib (all cycles)		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, and CMP should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 45 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 45 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients who discontinue study treatment regardless of reason for discontinuation will be followed for survival every 3 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of hedgehog pathway mutation (activating mutation of SMO or loss-of-function mutation of PTCH-1; see Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[g] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) occurring from the first treatment until 45 days after the last dose of study treatment will be captured in the eCRF.

[h] Study drug compliance will be reviewed with the patient.

[i] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[j] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Note: Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[l] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[m] Only if clinically indicated.

[n] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[o] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[p] Only if abnormal at baseline and if necessary to determine response to treatment.

[q] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[r] Only if abnormal at baseline.

Appendix 10
Alectinib in Patients with ALK Alterations

Treatment of patients with solid tumors that harbor anaplastic lymphoma kinase (ALK) alterations is part of the clinical trial outlined in the main protocol. This appendix contains details and study requirements that are specific to treatment with alectinib, including:

A10-4 MATERIALS AND METHODS

A10-4.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol. Listed here are additional requirements specific to treatment with alectinib.

A10-4.1.1 Additional Inclusion Criteria

- Patients with solid tumors that harbor ALK gene rearrangements as determined by next generation sequencing (NGS) or fluorescence in situ hybridization (FISH) using the Vysis ALK Break Apart FISH Probe Kit will be accepted.
- Putative activating non-synonymous mutations in and around the ALK kinase domain (amino acid 1062-1311) as determined by NGS
- Patients with ALK copy number gain as determined by NGS
- Melanoma patients with high ALK expression by IHC or presence of ALK-alternative transcription initiation (ALK^{ATI}) transcript (exon 1-19, intron 19, exon 20-29).
- For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<1\%$ per year during the treatment period and for at least 90 days after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with

no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

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

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

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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 information regarding specific testing methodologies and allowable identified mutations, see Appendix 5.

A10-4.1.2 Additional Exclusion Criteria

- ALK-positive NSCLC, neuroblastoma, and childhood tumors
- Previous treatment with alectinib or any other ALK inhibitor
- Patients with symptomatic bradycardia
- Administration of strong/potent CYP3A4 inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib
- Inability to swallow pills
- Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude absorption of alectinib

A10-4.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (Section 4.2).

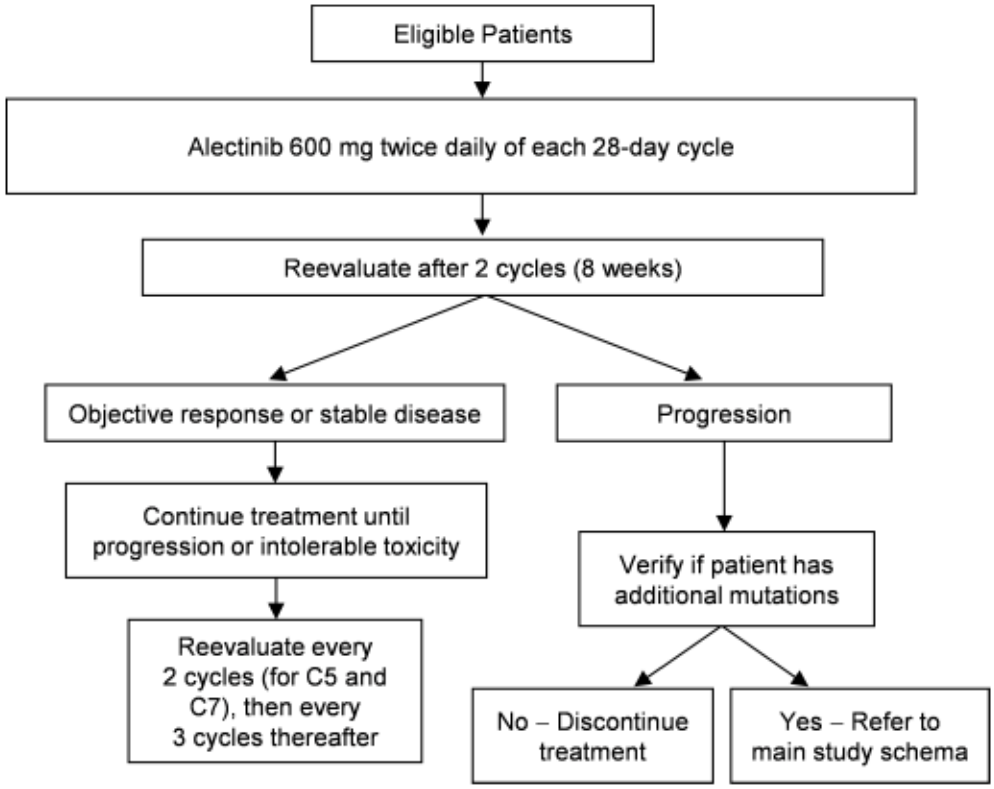
A10-4.3 STUDY TREATMENT

All patients will receive treatment with alectinib given twice daily at a dose of 600 mg orally (PO) in cycles of 28 days (4 weeks) duration. A schema of the study design is presented in A10-Figure 1.

All patients will receive:

- Alectinib 600 mg PO twice daily (BID; with food)
- No routine premedications are required.

A10-Figure 1: Study Schema: Alectinib



C=cycle.

A10-4.3.1 Alectinib (Alecensa®)

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. In nonclinical studies, alectinib inhibited 231 ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, 232 and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations.

a. Formulation

Alectinib comes in a hard capsule dosage form containing the following active ingredient:

[Chemical name] 9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloride

Each capsule contains 150 mg of alectinib (as free base) along with lactose monohydrate, carmellose calcium, hydroxypropyl cellulose, sodium lauryl sulfate (SLS) and magnesium stearate as excipients.

The formulation contains SLS as an excipient. This excipient is known to be associated potentially with gastrointestinal adverse events such as nausea, vomiting, diarrhea, and abdominal pain.

Additional information can be found in the Alecensa® U.S. Package Insert and the Alectinib Investigator's Brochure.

b. Dosage, Administration, and Storage

Alectinib 600 mg (four 150 mg capsules) should be administered PO BID with food in the morning and evening. If a dose is missed, patients should take the next dose at the scheduled time. Patients should not take two doses at the same time to make up for a missed dose.

Storage

Alectinib capsules should be stored in accordance with the storage instructions on the label.

c. Dosage Modification

Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of alectinib. Once a dose level reduction has occurred, the dose level may not be re-escalated. See A10-Table 1 for the alectinib dose reduction schedule. General dose modification advice for alectinib is provided in A10-Table 2.

A10-Table 1: Alectinib Dose Reduction Schedule

Dose reduction schedule	Dose level
Starting Dose	600 mg BID
First dose reduction	450 mg BID
Second dose reduction	300 mg BID

BID = twice daily.

If further dose reduction is indicated after two dose -reductions, the patient must discontinue alectinib. Administration of a dose below 300 mg BID is not allowed.

If alectinib has been withheld for > 21 days because of toxicity, the patient should be discontinued from alectinib. Alectinib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) in consultation with the Medical Monitor. The investigator and the Sponsor will determine the acceptable length of treatment interruption.

A10-Table 2: Alectinib Dose Modifications for Specific Adverse Events

Criteria	Dose Modification
ALT or AST elevation of greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 3 times ULN, then resume at reduced dose as per A10-Table 1.
ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue alectinib.
Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then resume at reduced dose as per A10-Table 1.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue alectinib.
Grade 3 renal impairment	Temporarily withhold until serum creatinine recovers to less than or equal to 1.5 times ULN, then resume at reduced dose as per A10-Table 1.
Grade 4 renal impairment	Permanently discontinue alectinib.
Symptomatic bradycardia	Withhold alectinib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume alectinib at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume alectinib at reduced dose (see A10-Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.

Criteria	Dose Modification
Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue alectinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume alectinib at reduced dose (see A10-Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue alectinib in case of recurrence.
CPK elevation greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose as per dose reduction schedule (A10-Table 1)
Hemolytic Anemia	Withhold alectinib if hemolytic anemia is suspected. Upon resolution, resume at reduced dose or permanently discontinue.
[a] Heart rate less than 60 beats per minute (bpm)	

d. Alectinib Warnings and Precautions

Hepatotoxicity

Elevations of AST greater than 5 times the upper limit of normal (ULN) occurred in 4.6% of patients, and elevations of ALT greater than 5 times the ULN occurred in 5.3% of 405 patients that received a dose of 600 mg BID. Elevations of bilirubin greater than 3 times the ULN occurred in 3.7% of patients. The majority (69% of the patients with hepatic transaminase elevations and 68% of the patients with bilirubin elevations) of these events occurred during the first 3 months of treatment. Six patients discontinued alectinib for Grade 3–4 AST and/or ALT elevations, and 4 patients discontinued alectinib for Grade 3 bilirubin elevations. Two patients with Grade 3–4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. Concurrent elevations in ALT or AST greater than or equal to 3 times the ULN and total bilirubin greater than or equal to 2 times the ULN, with normal alkaline phosphatase, occurred in less than 1% of patients treated with alectinib across clinical trials. Three patients with Grades 3–4 AST/ALT elevations had drug-induced liver injury (documented by liver biopsy in two cases).

Monitor liver function tests including ALT, AST, and total bilirubin according to the schedule of assessments and then once a month as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations.

Based on the severity of the adverse drug reaction, withhold alectinib and resume at a reduced dose, or permanently discontinue (refer to A10-Table 2).

Renal Impairment

Renal impairment occurred in 8% of patients exposed to alectinib in clinical trials. The incidence of Grade ≥ 3 renal impairment was 1.7%, of which 0.5% were fatal events. Dose modifications for renal impairment were required in 3.2% of patients. Median time to Grade ≥ 3 renal impairment was 3.7 months (range 0.5 to 14.7 months).

Permanently discontinue alectinib for Grade 4 renal toxicity. Withhold alectinib for Grade 3 renal toxicity until recovery to less than or equal to 1.5 times ULN, then resume at reduced dose (refer to A10-Table 2).

Interstitial lung Disease (ILD)/Pneumonitis

ILD/pneumonitis occurred in three (0.7%) patients exposed to alectinib in clinical trials and severe ILD (Grade 3) occurred in one (0.2%) of these patients.

Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold alectinib treatment in patients diagnosed with ILD/pneumonitis and permanently discontinue alectinib if no other potential causes of ILD/pneumonitis have been identified.

Bradycardia

Symptomatic bradycardia can occur with alectinib. Cases of bradycardia have been reported in 8.6% of patients treated with alectinib in clinical trials. Eighteen percent of 365 patients treated with alectinib for whom serial ECGs were available had heart rates of less than 50 bpm.

Monitor heart rate and blood pressure regularly. Dose modification is not required in cases of asymptomatic bradycardia. In cases of symptomatic bradycardia that is not life-threatening, withhold alectinib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above and evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If attributable to a concomitant medication, resume alectinib at a reduced dose (see Table 2) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue alectinib in case of recurrence. Permanently discontinue alectinib in cases of life-threatening bradycardia if no contributing concomitant medication is identified.

For management of symptomatic bradycardia, refer to A10-Table 2.

Severe Myalgia and Creatine Phosphokinase (CPK) Elevation

Postmarketing experience with some TKIs includes reports of myopathy and rhabdomyolysis (Hohenegger 2012).

Myalgia or musculoskeletal pain occurred in 26% of patients exposed to alectinib in clinical trials. The incidence of Grade 3 myalgia/musculoskeletal pain was 0.7%. Dose modifications for myalgia/musculoskeletal pain were required in 0.5% of patients.

Elevations of CPK occurred in 41% of 347 patients with CPK laboratory data available in patients exposed to alectinib in clinical trials. The incidence of Grade 3 elevations of CPK was 4.0%. Median time to Grade 3 CPK elevation was 14 days (interquartile range 13–28 days). Dose modifications for elevation of CPK occurred in 3.2 % of patients.

Blood CPK increases, generally Grades 1 and 2, and muscular adverse events (AEs) have been reported with alectinib treatment in 29% and 43% of the patients in clinical trials, respectively. Grade 3 myalgia and CPK elevations have been reported with alectinib treatment in 1.2% and 4.6%, respectively, and were reversible upon dose reduction and interruption.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every 2 weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, withhold alectinib then resume or reduce dose (refer to A10-Table 2).

Photosensitivity

Photosensitivity to sunlight has been reported with alectinib administration. Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sun screen and lip balm (SPF ≥50) to help protect against potential sunburn.

Embryo-Fetal Toxicity

Alectinib may cause fetal harm when administered to a pregnant woman. When administrated to pregnant rats and rabbits, alectinib caused embryo-fetal toxicity. Therefore, women of child-bearing potential, and male patients who are partners of women of child-bearing potential, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of alectinib (see additional inclusion criteria in Section A10-4.1.1).

Hemolytic Anemia

If hemoglobin concentration is <10 g/dL (Grade ≥ 2) and hemolytic anemia is suspected, withhold alectinib and initiate appropriate laboratory testing, in accordance with local

clinical practice guidelines. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (refer to dose modification A10-Table 2) upon resolution with improvement of hemoglobin to Grade ≤1 or baseline or permanently discontinue alectinib.

In case of anemia of non-hemolytic mechanism, assessed as related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the Table 2 (AE management table).

A10-4.4 CONCOMITANT AND PROHIBITED THERAPIES

A10-4.4.1 Concomitant Therapy

Refer to the main body of the protocol (Section 4.4.1) for concomitant therapies allowed.

Permitted Therapy

Caution should be exercised when the following treatments or procedures are co-administered or performed during treatment with alectinib:

- For medications that are substrates of P-gp transporter or breast cancer resistance protein transporter, the investigator should use caution and monitoring when considering concomitant use of alectinib. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided. If co-administration cannot be avoided, it is recommended that signs for toxicity are carefully monitored (see table below).
- Acetaminophen up to 2 g/day

A10-4.4.2 Prohibited Therapy

The following restrictions apply during the entire duration of study treatment:

- No other investigational therapy should be given to patients.
- No concomitant cancer treatment of any type (including chemotherapy, biologic therapy, hormonal therapy, immunotherapy, herbal therapy, radiation therapy) should be administered at any time while the patient is taking study treatment. If such treatment is required, then the patient must first be withdrawn from the trial.
- Use of the following therapies (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) is prohibited during the study and for at least 14 days prior to initiation of alectinib, unless otherwise specified below.
  - Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid binding resins while on study treatment

List of Substrates and Inducers of P-gp Transporter

This representative list is not intended to be an exhaustive list. Each patient's concomitant medications should be carefully considered by the investigator with regard

to the risk-benefit for the particular patient and appropriate monitoring, including any concomitant medication, dose adjustment, or therapeutic alternatives, which should be determined by the investigator caring for the patient.

P-gp	
Substrates	Inducers
aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan	avasimibe, carbmazepine, phenytoin, rifampin, St John's wort, tipranavir

Adapted from Levien and Baker 2003; Zhang 2010; and FDA Guidance on Drug Interaction Studies (2012).
Also see: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ DevelopmentResources/ DrugInteractionsLabeling/ucm080499.htm; http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

A10-4.5 STUDY ASSESSMENTS

All patients should visit the study center on the days specified in A10-Table 3 of this appendix. Molecular profiling reports must be seen and reviewed by the investigator prior to proceeding with other study-specific assessments. The complete schedule of assessments for patients receiving alectinib is contained in the study flowchart of this appendix. Baseline medical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), complete blood counts (CBCs), comprehensive metabolic profile (CMP; which includes LFTs [AST, ALT, and bilirubin]), creatine phosphokinase (CPK), and electrocardiogram (ECG) should be done ≤21 days prior to initiation of treatment. If the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1, they do not have to be repeated on Day 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and tumor markers to document measurement of disease must be performed ≤4 weeks prior to initiation of treatment.

A10-4.5.1 Descriptions of Study Assessments

Refer to the main body of the protocol (Section 4.5.1) for details.

A10-4.5.1.1 Alectinib-Specific Study Assessments

- Optional Tumor Tissue Samples (Archival and End of Treatment/Disease Progression):

  Collection of a sample of archived tumor biopsy specimen (if available) is highly encouraged. Additionally, an optional tissue sample collected at end of treatment/disease progression may be submitted, if available.

  Although any tumor tissue material can be submitted, it is encouraged to submit tissue as follows:

  – Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)

- Ideally, submission of 15, but not less than 10, serial, unstained, positively charged glass slides prepared from FFPE tumor blocks and 4μm thickness
- Presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.

A10-4.5.2 Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of ALK alterations as outlined in Appendix 5 (should occur prior to obtaining other study-specific assessments). For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- ECOG PS
- Blood Pressure and Heart Rate
- ECG
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Collection of archival tumor tissue, optional
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis
- PET scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

A10-4.5.3 Assessments during Treatment

Patients will visit the study center once every 4 weeks (±72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will

occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 7, Day 1, subsequent visits will be every 12 weeks, with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1

- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3

- Adverse event (AE) evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP every 2 weeks for 3 months (Cycles 1–3) and as clinically indicated
- CPK every 2 weeks for first month (Cycle 1), then Day 1 of Cycles 2 and 3
- ECG (Cycle 1 and Cycle 3)
- Blood pressure and heart rate

c. Day 1 of Cycle 3

- Plasma biomarker collection
- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)

d. Day 1 of Cycles 5

- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or other protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)
- Review study drug compliance with patient
- CMP
- CPK
- ECG
- Blood pressure and heart rate

e. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or other protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Tumor markers (only if clinically indicated)
- ECG (Day 1 of Cycle 7 only)
- Blood pressure and heart rate
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

A10-4.5.4 End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of alectinib. The following assessments will be conducted at the visit:

- Plasma biomarker collection
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

- At disease progression, an optional FFPE tissue sample may be submitted for exploratory research, if available.

If the patient's worsening disease combined with travel distance makes the safety follow up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

A10-4.5.5 Follow-Up Assessments

Please refer to the main body of the protocol for the follow-up assessments.

A10-4.6 PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

A10-4.7 PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST

Please refer to Section 5.2.3 in the main body of the protocol for protocol-defined adverse events of special interest.

Appendix 10
Alectinib in Patients with ALK Alterations (cont.)

A10-Table 3: Alectinib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
Tests and Observations							
Informed consent [e]	x						
Obtain/review molecular profiling report/ pathology report [f]	x						
Medical history	x						
ECOG PS	x						
Blood pressure and heart rate	x	x	x	x			
ECG	x	x [g] [Day 1 of Cycles 1 and 3 only]	x [g]	x [g] (Day 1 of Cycle 7 only)			
Adverse event evaluation (all cycles) [h]		x	x	x	x		
Study drug compliance review [i]		x	x	x	x		
Survival status							x

Appendix 10
Alectinib in Patients with ALK Alterations (cont.)

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c]	
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		(±14 Days)	Survival [d] (±14 Days)
Laboratory evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP [j]	x	x (every 2 weeks for the first 3 months [Cycle 1–Cycle 3])	x	x	x		
CPK	x	x (every 2 weeks for first month [Cycle 1], then Day 1 of Cycles 2 and 3)	x	x	x		
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x		
Pregnancy test [k]	x						
Molecular profiling results [l]		x					
Archival tumor sample, optional	x [m]				x [m]		
Staging							
Tumor markers [n]	x		x	x	X	x	

Appendix 10
Alectinib in Patients with ALK Alterations (cont.)

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
CT scan of chest, abdomen, and pelvis [o]	x		x [p]	x [p]	x [p]	x	
PET scan or bone scan [o]	x [n]			x [q]			
Head CT or MRI scan [o]	x [r]			x [s]			
Treatment							
Alectinib (all cycles)		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, and ECG should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients who discontinue study treatment regardless of reason for discontinuation will be followed for survival every 3 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of ALK alterations (see Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[g] Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1.

[h] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[i] Study drug compliance will be reviewed with the patient.

[j] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[k] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed ≤7 days prior to first dose of trial treatment.

[l] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[m] Archival tissue will be requested and collected for future correlative research studies, if available and with specific consent. The sample can be provided during or after screening while the patient is on study. An optional tissue sample collected at end of treatment / disease progression can be submitted, if available.

[n] Only if clinically indicated.

[o] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[p] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[q] Only if abnormal at baseline and if necessary to determine response to treatment.

[r] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[s] Only if abnormal at baseline.

Appendix 11
Atezolizumab for Patients with Cancers Characterized by PD-L1 Copy Number Gain, Deficiency in Mismatch Repair Enzymes, High Levels of Microsatellite Instability, and Elevated Tumor Mutational Burden and/or Alterations of DNA Proofreading/Repair Genes

Treatment of patients with solid tumors that are characterized by PD-L1 copy number gain, deficiency in mismatch repair enzymes (dMMR), high levels of microsatellite instability (MSI-H), elevated tTMB, and/or alterations of DNA proofreading/repair genes (e.g., POLE, POLD1). This appendix contains details and study requirements that are specific to treatment with atezolizumab, including:

A11-4 MATERIALS AND METHODS

A11-4.1 PATIENTS

Eligible patients must meet all of the eligibility requirements contained in the main study protocol. Listed here are all requirements specific to treatment with atezolizumab.

A11-4.1.1 Full Inclusion Criteria

- Able to understand the nature of this trial and provide written informed consent
- Age ≥ 18 years
- Willing and able to comply with study and follow-up procedures
- Life expectancy ≥ 12 weeks
- Histologically documented cancer with evidence of metastasis (solid tumors, not including hematologic malignancies). Patients with locally advanced, unresectable tumors may be eligible following approval of the medical monitor.

- Molecular testing results used for patient eligibility should be obtained from the most recent tumor biopsy. If molecular testing is not available from the most recent tumor biopsy, but all eligibility criteria are otherwise fulfilled, the patient can be enrolled based on the available molecular testing result. In these cases:1) a tissue sample from the most recent tumor biopsy must be provided for central re-testing, if available 2) additionally, a tissue sample from the orginal archival biopsy tested for enrollment must be provided for central re-testing, if available. Alternatively and for selected arms, molecular testing results used to determine patient eligibility could have been obtained from a recent blood sample (up to 2 months prior to enrollment) (see Appendix 5 for specific requirements) described in the study design.
- Patients who have received standard first-line therapy for metastatic cancer (except where no first-line therapy exists or, following approval by the medical monitor, in patients enrolling with locally advanced unresectable disease) in whom a trial of targeted therapy is considered the best available treatment option. Eligible patients should not have available approved therapies that would convey clinical benefit or such approved therapies are not considered suitable options per the treating physician's judgement
- No previous treatment with the specific assigned study drug or any other drug sharing the same target
- Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Appendix 4)
- Patients with elevated tissue tumor mutational burden (tTMB) (≥ 10 mutations/Mb as determined using any CLIA validated assay; see Appendix 5 for details). For tissue requirements; refer to A11-4.5.1.2.1
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (see Appendix 1).

  ECOG PS score must be documented ≤21 days prior to first treatment and confirmation of ECOG PS must be entered into the interactive web response system (IWRS) prior to initiation of treatment.
- Adequate hematologic function defined as the following:
  - Absolute neutrophil count (ANC) ≥ 1500/μL
  - Hemoglobin (Hgb) ≥ 9 g/dL (may be achieved with erythropoietin agents or transfusions)
  - Platelets ≥ 100,000/μL
- Adequate renal and liver function defined as the following:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5× the upper limit of normal (ULN) (≤5× ULN if considered due to primary or metastatic liver involvement)

- Total bilirubin ≤1.5× ULN
- Alkaline phosphatase <2.5× ULN (<5× ULN if considered due to tumor)
- Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥40 mL/min by Cockcroft-Gault formula

  Glomerular filtration rate estimation:
  {(140 – age) × (weight [in kg]) /
  (72 × serum creatinine [in mg/dL])} × 0.85 (if female)

- Serum albumin ≥25 g/L (2.5 g/dL)
- For patients not receiving therapeutic anticoagulation: International Normalized Ratio (INR) or aldosterone–plasma renin activity ratio (aPRR) ≤1.5× ULN.
- Male patients with prostate cancer who are receiving androgen blockade will be eligible for the study.
- Female patients of childbearing potential must agree to use acceptable methods of contraception.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods 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.

  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, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

A11-4.1.2 Full Exclusion Criteria

- Patients with hematologic malignancies
- Concurrent administration of any other anti-cancer therapy (except male patients with prostate cancer who are receiving androgen blockade):
  - Bisphosphonates and denosumab are allowed.

  - Most recent anti-cancer therapy ≤ 28 days or have not recovered from the side effects, excluding alopecia or mild residual neuropathy. Patients with alopecia or mild residual neuropathy may be eligible after discussion with the Medical Monitor
  - Radiation therapy within ≤ 14 days
- History of carcinomatous meningitis
- Uncontrolled concurrent malignancy (early stage is allowed if not requiring active therapy or intervention)
- Pregnant or breastfeeding, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.
- Any of the following cardiovascular events within 6 months prior to study entry: myocardial infarction, malignant hypertension, severe/unstable angina, symptomatic congestive heart failure, cerebral vascular accident, or transient ischemic attack
- Pulmonary embolism within 30 days prior to study entry
- History or presence of clinically significant ventricular or atrial dysrhythmia > Grade 2
  - Patients with chronic, rate-controlled atrial arrhythmias who do not have other cardiac abnormalities are eligible.
- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of treated CNS metastases are eligible, provided all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS
  - Minimal neurologic symptoms
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - Metastases limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord)
  - Evidence of stable disease (for at least 1 month)
  - No evidence of interim progression between completion of CNS-directed therapy and the screening brain scan
  - No stereotactic radiotherapy or whole-brain radiotherapy within 14 days prior to initiation of study treatment
  - No ongoing requirement for corticosteroids as therapy for CNS disease (anticonvulsants at a stable dose are allowed)

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- History of leptomeningeal disease
- Uncontrolled tumor-related pain

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

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
- Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)
- Previous treatment with atezolizumab or another PD-1/PD-L1 inhibitor
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- 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, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see A11-Table 1 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 thyroid-replacement hormone are eligible for the study
  - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study

  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

    Rash must cover < 10% of body surface area

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

    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

  - Transient autoimmune manifestations of an acute infectious disease (e.g., acute Lyme arthritis) that resolved upon treatment of the infectious agent

- Prior allogeneic stem cell or solid organ transplantation
- 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.
- Positive HIV test at screening
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
  - If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening
  - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- 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 oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- 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 course of the study; the determination of 'major' is at the discretion of the treating physician.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study or within 5 months after the final dose of atezolizumab
- History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year overall survival [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
- Any other acute or chronic medical or psychiatric condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2 [IL-2]) within 4 weeks or five half-lives of the drug (whichever is longer) prior to Cycle 1 Day 1.
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after discussion with and approval by the Medical Monitor.
  - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol

A11-Table 1 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 • 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 cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

A11-4.2 METHOD OF TREATMENT ASSIGNMENT

Please refer to the main body of the protocol for the methods of treatment enrollment and study drug procurement (Section 4.2).

A11-4.3 STUDY TREATMENT

All patients will receive treatment with atezolizumab, given intravenously (IV) in cycles of 21 days (3 weeks) duration. A schema of the study design is presented in A11-Figure 1.

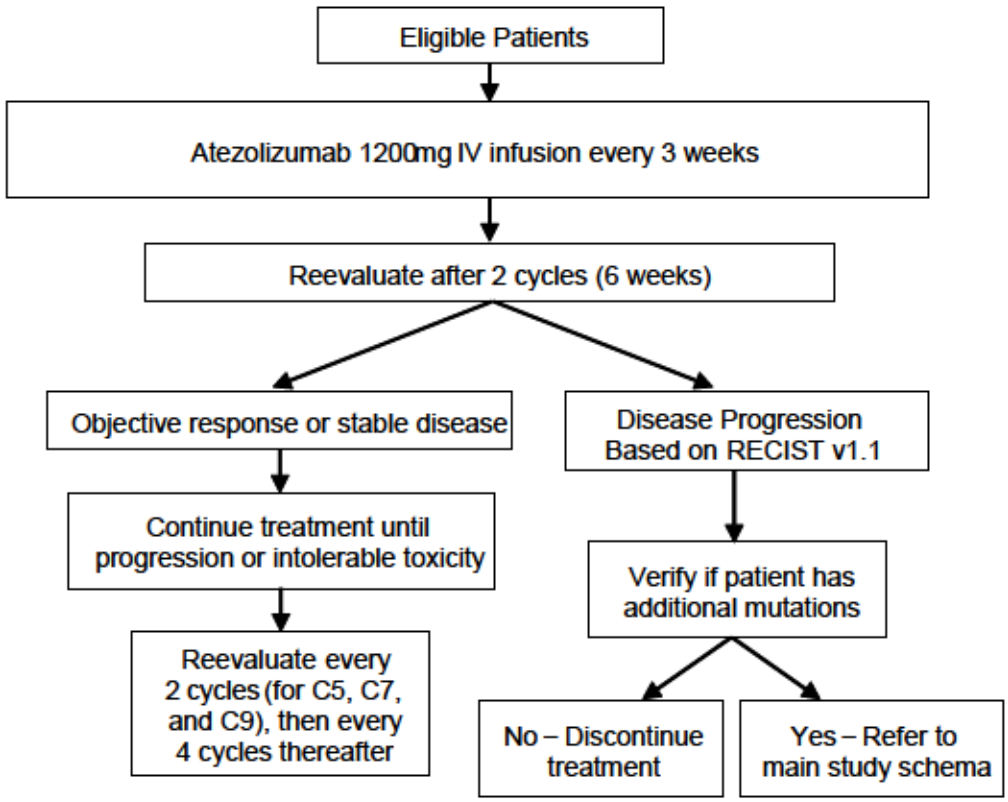
All patients will receive:

- Atezolizumab (fixed dose of 1200 mg) intravenously on day 1 of each 21-day cycle

- No routine premedications are required; however, patients who experience infusion-related symptoms may be premedicated as per standard institutional practice for subsequent infusions.

For additional information regarding the dosage and administration of atezolizumab, please see Section A11-4.3.1b of this appendix.

A11-Figure 1: Study Schema: Atezolizumab



C = cycle. RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1.
Note: At the discretion of the treating physician and after discussion with the Medical Monitor, treatment with atezolizumab may be continued beyond progression if the anticipated clinical benefit outweighs the risk.

A11-4.3.1 Atezolizumab (Tecentriq™)

a. Formulation

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution. The atezolizumab drug product is provided in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in a solution containing histidine acetate, sucrose, and polysorbate 20 at pH 5.8.

b. Dosage, Administration, and Storage

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator. 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 equipment needed and procedure to be followed in case of suspected anaphylaxis associated with atezolizumab infusion, see Appendix 12. Atezolizumab infusions will be administered per the instructions outlined in the table below.

A11-Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) 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, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded 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 recorded during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of infusion-related reactions (IRRs) and cytokine-release syndrome are provided in the Appendix 13.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section A11-4.3.1d and in Appendix 13.

Storage

The atezolizumab drug product must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. The atezolizumab drug product should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light.

c. Management of Toxicities

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below.

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 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. 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. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous reactions. *In addition,* immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis. Refer to Appendix 13 of this protocol and to Section 6 the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

d. Management of Patients Who Experience Specific Adverse Events

Dose Modifications

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

Treatment Interruption

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone 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 investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The

acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Management Guidelines

Guidelines for management of patients who experience specific adverse events associated with atezolizumab, including infusion-related reactions and immune-mediated events (e.g., pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, neurologic, and renal events), are provided in Appendix 13.

A11-4.4 CONCOMITANT AND EXCLUDED THERAPIES

A11-4.4.1 Concomitant Therapy

Please refer to the main body of the protocol (Section 4.4.1) for concomitant therapies allowed.

A11-4.4.2 Cautionary Therapy

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance) (see also Section A11-4.1.2).

Systemic corticosteroids are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy. Guidelines for the management of immune-mediated adverse events are described in the Atezolizumab Investigator's Brochure.

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. Their use for patients on this study is allowed at the discretion of the investigator, however the herbal therapy must have no known interactions with any study treatment nor can it be used specifically for the treatment of cancer (see Section A11-4.4.3).

A11-4.4.3 Excluded Therapy

The following restrictions apply during the entire duration of study treatment:

- 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 drug, depending on the anti-cancer agent (see Section A11-4.1.2) and during study treatment until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab. Note that vaccinations (such as influenza, COVID-19) are permitted as long as they are not live, attenuated.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

A11-4.5 STUDY ASSESSMENTS

All patients should visit the study center on the days specified in A11-Table 3 of this appendix. Molecular profiling reports must be seen and reviewed by the investigator prior to proceeding with other study-specific assessments. The complete schedule of assessments for patients receiving atezolizumab is contained in the study flowchart of this appendix. Baseline medical history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), complete blood counts (CBC), and comprehensive metabolic profile (CMP) should be done ≤21 days prior to initiation of treatment. If the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1, they do not have to be repeated on Day 1. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and tumor markers (if applicable) to document measurement of disease must be performed ≤4 weeks prior to initiation of treatment.

A11-4.5.1 Descriptions of Study Assessments

A11-4.5.1.1 General Study Assessments

See Section 4.5.1 in the main body of the protocol for descriptions of the assessments.

A11-4.5.1.2 Atezolizumab-Specific Study Assessments

A11-4.5.1.2.1 Atezolizumab-Specific Laboratory and Other Biological Samples

In addition to overall study-related laboratory assessments, the following laboratory samples are required for patients receiving atezolizumab:

- Serum samples for CRP (to be performed by study sites; only for patients enrolled under Version 6 of the protocol and later)
- Serum samples for PK/ADA assessments (only for patients enrolled under Version 6 of the protocol and later)
    - PK and ADAs will be assessed using validated assays and will be performed by a central facility or by the Sponsor.
- Whole blood sample for normal control DNA analysis for WES (performed by the Sponsor; only for patients enrolled under Version 6 of the protocol and later)
- Tumor tissue sample for biomarker analyses (performed by the Sponsor). Requirements are based on whether the patient had molecular testing done using the FoundationOne/FoundationOne CDx assay or not. Requirements are as follows:

1) Archival or New Pre-treatment Tumor Tissue Requirements

A) If molecular testing <u>WAS NOT</u> performed using FoundationOne or FoundationOne CDx, submission of an archival and/or new pretreatment tissue sample is <u>mandatory</u>:

- Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)
- Ideally, submission of 15, but at least 10 serial, unstained, positively-charged glass slides prepared from FFPE tumor blocks at 4μm thickness is required.
- Total tissue volume submitted should measures ideally 0.6 mm^3 but at least 0.2 mm^3 and presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.
- On a case-by-case basis and upon approval by the Medical Monitor, patients with fewer slides/tissue available could be enrolled if the total tissue volume submitted measures ideally 0.6 mm^3 but at least 0.2 mm^3 with a minimum of 20% confirmed viable tumor content.

B) If molecular testing WAS performed using FoundationOne or FoundationOne CDx, an archival or new pretreatment tissue sample must be submitted, if available:

- Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)
- Ideally, submission of 15, but not less than 5 serial, unstained, positively-charged glass slides prepared from FFPE tumor blocks at 4um thickness is requested.
- Presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.

C) If molecular testing WAS NOT performed on the most recent tissue biopsy, irrespective of assay used, submission of the most recent pretreatment tissue sample is required, if available. Additionally, a tissue sample from the original archival biopsy tested for enrollment must be provided for central re-testing, if available:

- Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)
- Ideally, submission of 15, but at least 10 serial, unstained, positively-charged glass slides prepared from FFPE tumor blocks at 4μm thickness is required.
- Total tissue volume submitted should measures ideally 0.6 mm^3 but at least 0.2 mm^3 and presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.
- On a case-by-case basis and upon approval by the Medical Monitor, patients with fewer slides/tissue available could be enrolled if the total tissue volume submitted measures ideally 0.6 mm^3 but at least 0.2 mm^3 with a minimum of 20% confirmed viable tumor content.

2) Optional tissue samples: new pre-treatment, on-treatment (Cycle 2, Day1), and end of study tissue sample requirements

A new pre-treatment tissue biopsy is highly encouraged, but not required, for all patients with molecular profile data obtained from biopsies that were collected more than 6 months prior to enrollment.

An on-treatment biopsy may be collected at Cycle 2, Day 1 and at end of study or disease progression to enable exploratory biomarker analyses. If multiple lesions are available, the same tumor lesion should be biopsied at all timepoints, if feasible.

Although any tumor tissue material can be submitted, it is encouraged to submit tissue as follows:

- Formalin-fixed, paraffin-embedded (FFPE) tissue blocks (preferred)
- Ideally, submission of 15, but not less than 5, serial, unstained, positively charged glass slides prepared from FFPE tumor blocks and 4μm thickness
- Total tissue volume submitted should measure ideally 0.6 mm^3 but at least 0.2 mm^3 and presence of at least 20% viable tumor content should be confirmed prior to submission of tissue samples. Samples should have preserved cellular context and tissue architecture, regardless of needle gauge (18 gauge or larger) or retrieval method.
- Additional residual material (e.g. DNA, RNA) may be requested from sites to enable exploratory biomarker research, as appropriate and if available.

For information on storage and use of PK and ADA samples, see below. For information on storage and use of all other laboratory samples, see Section 4.5.1.4 of protocol.

Any remaining samples collected for PK or ADA may be used for exploratory biomarker profiling, identification, and pharmacodynamics assay development purposes and additional safety assessments (e.g., ADA assay) as appropriate.

Use and storage of remaining PK and/or ADA samples from study-related procedures: the remaining samples obtained for study-related procedures may be retained for up to 5 years after the final study report finalization.

A11-4.5.1.2.2 Patient-Reported Outcomes

For patients enrolled under Version 6 of the protocol and later, PRO data will be collected with the EORTC scales (see Appendix 14) using paper questionnaires to document the treatment benefit of atezolizumab. The questionnaire, translated into the local language as appropriate, will be completed at specified timepoints during the study. This assessment is required prior to administration of study drug and prior to any other study assessment(s) that could bias patients' responses to the questions in order to ensure that data quality meet regulatory requirements. Study personnel should review all questions for completeness before the patient leaves the investigational site, and the hard copy originals of the questions must be maintained as part of the patient's medical record at the site for source data verification.

The EORTC item bank is comprised of items from the EORTC QLQ C30 and disease-specific modules to capture five aspects of patient functioning (physical, emotional, role, cognitive, and social), quality of life and a variety of symptoms that could be experienced

due to the primary tumor, metastases or treatments. The recall period is of the previous week and the rating is done on either a 4-point scale except when assessing quality of life, which uses a 7-point scale. Scales were selected to capture various aspects of the treatment impact on patients while reducing questionnaire completion burden.

A11-4.5.2 Screening and Pretreatment Assessments

- Written Informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of elevated tTMB (should occur prior to obtaining other study-specific assessments)
- Medical history
- Vital signs
- ECOG PS (must be performed within 21 days of Cycle 1, Day 1). Confirmation of ECOG PS must be entered into the IWRS at the time of enrollment.
- ECG
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody (HBsAb), and total HBcAb
  - If a patient has a negative HBsAg result and a positive total HBcAb result, 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 active HCV infection
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Urinalysis
- Confirm availability of an archival or new pretreatment tissue sample (refer to A11-4.5.1.2.1 for tissue requirements)
- Tumor markers (only if clinically indicated)

- CT scans of the chest, abdomen, and pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

A11-4.5.3 Assessments during Treatment

Patients will visit the study center once every 3 weeks on the day of each scheduled treatment (±72 hours). Protocol treatments will continue until tumor progression or intolerable toxicity occurs. The following assessments will be performed:

a. Day 1 of Every Cycle

- Vital signs
- ECOG status
- ECG, if clinically indicated
- Hematology
- Chemistry
- Urinalysis (only if clinically indicated)
- Adverse event (AE) evaluation (see Study Flowchart A11-Table 3 for details)
- Concomitant medication evaluation (only collected for patients enrolled under Version 6 of the protocol and later)

b. Day 1 of Cycle 1

- Plasma/serum biomarker collection (pre-dose)
- Thyroid function testing
- Whole blood sample collection (normal germline DNA control; only collected for patients enrolled under Version 6 of the protocol and later) (pre-dose)
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)
- Serum sample for CRP assessment (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

c. Day 1 of Cycle 2

- Optional tissue sample collection (FFPE) for future exploratory analysis (see A11-4.5.1.2.1 for tissue requirements)
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

d. Day 1 of Cycle 3

- Plasma/serum biomarker collection (pre-dose)
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)
- Serum sample for CRP assessment (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

e. Day 1 of Cycles 3 and 5

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline). For patients enrolled under Version 6 of the protocol or later, scans for response assessment must be submitted for IRC review.

f. Day 1 of Cycle 4

- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

g. Day 1 of Cycle 4 and Every Three Cycles Thereafter

- Thyroid function testing
- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

h. Day 1 of Cycle 7

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline), or MRI as clinically indicated.
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

i. Day 1 of Cycle 8

- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

j. Day 1 of Cycle 12

- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

k. Day 1 of Cycle 13 and Every Six Cycles Thereafter (*or sooner if clinically indicated*)

- *Tumor markers (only if clinically indicated)*
- *Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline).*
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

l. Day 1 of Cycle 16

- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

A11-4.5.4 End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of atezolizumab. The following assessments will be conducted at the follow-up visit:

- Vital signs
- ECOG status
- Hematology
- Chemistry
- Coagulation
- Thyroid function testing
- Plasma biomarker collection
- Serum sample collection for PK and ADA analyses (only collected for patients enrolled under Version 6 of the protocol and later)
- Serum sample for CRP assessment (only collected for patients enrolled under Version 6 of the protocol and later)
- AE evaluations (see Study Flowchart A11-Table 3 for details)
- Concomitant medication evaluation (only collected for patients enrolled under Version 6 of the protocol and later)
- Urine or serum pregnancy test – Any positive urine pregnancy test must be confirmed by a serum pregnancy test.

- Optional tissue sample collection (FFPE) for future exploratory analysis (see A11-4.5.1.2.1 for tissue requirements)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (only scans that were abnormal at baseline).
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs and concomitant medications. Alternatively, the patient's local physician may be contacted to collect AE data, concomitant medications and any standard of care laboratory and CT data, if performed.

A11-4.6 PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

A11-4.7PROTOCOL-DEFINED ADVERSE EVENTS OF SPECIAL INTEREST (ATEZOLIZUMAB)

Please refer to Section 5.2.3 in the main body of the protocol for protocol-defined adverse events of special interest.

Appendix 11
Atezolizumab for Patients with Cancers Characterized by PD-L1 Copy Number Gain, Deficiency in Mismatch Repair Enzymes, High Levels of Microsatellite Instability, High Tumor Mutational Burden, and/or Alterations of DNA Proofreading/Repair Genes (cont.)

A11-Table 3: Atezolizumab Study Flowchart

Assessments	Pre-Treatment	Trial Treatment					End of Treatment Safety Follow-Up [c]
		All Cycles	Reassessments				
	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	C4, D1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	C13, D1 (and Every 6 Cycles After, *or as clinically indicated*) [b] (±3 Days)	
Tests and Observations							
Informed consent	x						
Obtain/review molecular profiling report/ pathology report [d]	x						
Medical history	x						
Vital signs [e]	x	x					x
ECOG PS	x (within 21 days of C1D1)	x					x
ECG [f]	x	x					
Adverse event and concomitant medication evaluation [g]	x	x					x

Appendix 11
Atezolizumab for Patients with Cancers Characterized by PD-L1 Copy Number Gain, Deficiency in Mismatch Repair Enzymes, High Levels of Microsatellite Instability, High Tumor Mutational Burden, and/or Alterations of DNA Proofreading/Repair Genes (cont.)

	Pre-Treatment	Trial Treatment					
		All Cycles	Reassessments				
Assessments	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	C4, D1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	C13, D1 (and Every 6 Cycles After, *or as clinically indicated*) [b] (±3 Days)	End of Treatment Safety Follow-Up [c]
Laboratory Evaluations							
Hematology [h]	x [i]	x [j]					x
Chemistry panel [k]	x [i]	x [j]					x
Coagulation (INR, aPTT)	x [i]						x
Thyroid function [l]	x [i]	x [C1 only]		x			x
Viral serology [m]	x [i]						
Urinalysis [n]	x [i]	x [o]					
Plasma/serum biomarkers		x [C1 only]	x [C3 only]				x
Serum CRP sample [p]		x [C1 and C3 only]					x
Whole blood sample (normal control DNA) [q]		x [C1 only]					
Pregnancy test [r]	x			x			X
Molecular profiling results [s]		x					

Appendix 11

Atezolizumab for Patients with Cancers Characterized by PD-L1 Copy Number Gain, Deficiency in Mismatch Repair Enzymes, High Levels of Microsatellite Instability, High Tumor Mutational Burden, and/or Alterations of DNA Proofreading/Repair Genes (cont.)

	Pre-Treatment	Trial Treatment					
		All Cycles	Reassessments				
Assessments	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	C4, D1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	C13, D1 (and Every 6 Cycles After, *or as clinically indicated*) [b] (±3 Days)	End of Treatment Safety Follow-Up [c]
Laboratory Evaluations (cont),							
Archival tumor sample or new pre-treatment biopsy [t])	x [t]						
Optional new tissue biopsy [u]	x [v]	C2 only					x
Serum PK *sample* [p]		x [Cycles 1,2,3,4,8, 12,16 only]					x
Serum ADA *sample* [p]		x [Cycles 1,2,3,4,8, 12,16 only]					x
Staging							
Tumor markers [u]	x		x		x	*x*	
CT scan of chest, abdomen, pelvis	x [w]		x [x]		x [x]	*x* [x]	x [x]
PET scan or bone scan	x [u]				x [y]	x [y]	
Head CT or MRI scan	x [z]				x [aa]	x [aa]	
Treatment							
Atezolizumab [bb]		x					

Appendix 11
Atezolizumab for Patients with Cancers Characterized by PD-L1 Copy Number Gain, Deficiency in Mismatch Repair Enzymes, High Levels of Microsatellite Instability, High Tumor Mutational Burden, and/or Alterations of DNA Proofreading/Repair Genes (cont.)

ADA = anti-drug antibody; C = cycle; CRP = C-reactive protein; CT = computerized tomography; D = day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IRC = independent review committee; MRI = magnetic resonance imaging; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus ; HCV = hepatitis C virus; PET = positron emission tomography; PK = pharmacokinetics.

[a] The medical history, physical examination, vital signs, weight, ECOG PS, Hematology and Chemistry panels should be done ≤ 21 days prior to initiation of treatment. However, if the Hematology and Chemistry panels are performed within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] *Assessments should be done every 6 cycles, or sooner if clinically indicated.*

[c] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles.

[d] Confirmation of eligible genetic alterations (see Appendix 5) should occur prior to performing other trial-related assessments.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, 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 the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

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

[g] For patients enrolled under Version 6 of the protocol or later, 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 in the eCRF. 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. For patients enrolled prior to Version 6 of the protocol, adverse events (see Section 5.2.1), protocol-defined events of special interest (see Section 5.2.3), and serious adverse events (except those unequivocally related to disease progression), will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, all deaths, regardless of cause, should be reported. , In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported. Concomitant medications should only be collected for patients enrolled under Version 6 of the protocol and later, and should be reported from ≤ 7 days prior to the first dose of study drug to the end-of-treatment visit and reported in the eCRF.

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

[i] Screening laboratory test results must be obtained within 21 days prior to initiation of study treatment.

[j] If Hematology and Chemistry panels are performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[k] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.

[l] 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 third cycle thereafter.

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

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

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

[p] Serum samples should only be collected from patients enrolled under Version 6 of the protocol or later. On days the patient receives study treatment, samples should be collected pre-dose.

[q] Sample collection is only required for patients enrolled under Version 6 of the protocol or later.

[r] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

[s] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[t] For patients receiving atezolizumab where molecular testing was not performed using FoundationOne or FoundationOne CDx, submission of an archival or new pretreatment tissue sample is mandatory. For patients receiving atezolizumab where molecular testing was performed using FoundationOne or FoundationOne CDx, submission of an archival or new pretreatment tissue sample is required, if available. The tissue sample must be submitted within 4 weeks after enrollment (refer to A11-4.5.1.2.1 for tissue requirements).

[u] Only if clinically indicated.

[v] A new pre-treatment tissue biopsy is highly encouraged, but not required, for all patients with molecular profile data obtained from biopsies that were collected more than 6 months prior to enrollment.

[w] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[x] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past *6* cycles.

[y] Only if abnormal at baseline and if necessary to determine response to treatment.

[z] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[aa] Only if abnormal at baseline.

[bb] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

Appendix 12
Anaphylaxis Precautions with Atezolizumab

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study treatment infusion.
2. 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 as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

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

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

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

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone 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). The acceptable length of treatment interruption must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. *COVID-19 evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
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 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, 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 Medical Monitor. [c] • *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. • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 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 the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in 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
Guidelines for patients without hepatocellular carcinoma	
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
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 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]

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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Guidelines for patients without hepatocellular carcinoma (cont.)	
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 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.
• Guidelines for patients with hepatocellular carcinoma	
• AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN • or • AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN • or • AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Monitor LFTs more frequently until return to baseline values. • For events of > 5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or 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 the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 2 Management Guidelines for Hepatic Events (cont.)

• Guidelines for patients with hepatocellular carcinoma (cont.)	
• Event	• Management
• AST or ALT increases to > 10 × ULN or total bilirubin increases to > 3 × ULN	• 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 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 baseline, taper corticosteroids over ≥ 1 month.

LFT = liver function test; ULN = upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. *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]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *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 the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor.[c] • Refer patient to GI specialist for evaluation and *confirmatory* biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed

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. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and 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.*
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).* • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for 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 the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

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 *drugs* such as methimazole or carbimazole as needed. • *Refer* to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact *the* Medical Monitor for 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 the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and 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 the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 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 *the* Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 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 Myocarditis

Event	Management
Immune-mediated myocarditis, *Grades* 2–4 *Immune-mediated pericardial disorders, Grades 2–4*	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider *antiarrhythmic* drugs, temporary pacemaker, ECMO, VAD *or pericardiocentesis* as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, *antipyretic medications*, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Severe SARS-CoV-2 infection 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 SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact *the* Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, *antipyretic medications*, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact *the* Medical Monitor.

Table 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 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 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 these 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, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, *antipyretic 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×ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase >2.0–5.0×ULN:** • Treat as 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 corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* were mild in severity and self-limiting, with or without pruritus.Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 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.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 9 Management Guidelines for Dermatologic Events (cont.)

Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact 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 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 patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 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.
Immune-mediated neuropathy, 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. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact *the* Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact *the* Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on *the investigator's* benefit–risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table **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 corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in *Table 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 patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in *Table 14*.

Table 14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • 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 patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 13 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]
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 patients with atezolizumab should be based on *the* investigator's benefit–risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
  - Platelet count $<100\times10^9$/L (100,000/μL)
  - ANC $<1.0\times10^9$/L (1000/μL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq181\times10^9$/L (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 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 14
European Organisation for Research and Treatment of Cancer (EORTC) Item Bank

ENGLISH

EORTC Scales

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

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

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Did you need to rest?	1	2	3	4
9. Have you felt weak?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
10. Were you tired?	1	2	3	4
11. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
12. Did you feel tense?	1	2	3	4
13. Did you worry?	1	2	3	4
14. Did you feel irritable?	1	2	3	4
15. Did you feel depressed?	1	2	3	4
16. Have you had difficulty remembering things?	1	2	3	4
17. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
18. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Please go on to the next page

ENGLISH

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
21.	How much did you cough?	1	2	3	4
22.	Did you cough up blood?	1	2	3	4
23.	Were you short of breath when you rested?	1	2	3	4
24.	Were you short of breath when you walked?	1	2	3	4
25.	Were you short of breath when you climbed stairs?	1	2	3	4
26.	Have you had pain in your chest?	1	2	3	4
27.	Have you had pain in your arm or shoulder?	1	2	3	4
28.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
29.	Did you take any medicine for pain?				
	1 No **2** Yes				
	If yes, how much did it help?	1	2	3	4
30.	To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

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