PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL, SINGLE-ARM, MULTI-COHORT, PROOF-OF-PRINCIPLE STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF COBIMETINIB AND ATEZOLIZUMAB IN ADVANCED RARE TUMORS.**
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TRIAL DRUG PROVIDED BY:	Genentech, Inc.
MEDICAL MONITOR:	UT MD Anderson Cancer Center (IND Office)
SPONSOR:	The University of Texas MD Anderson Cancer Center
PROTOCOL DATE:	March 6th 2020

MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2016-0869
Protocol Title	A Phase II, Open-label, Single-arm, Multi-cohort Proof-of-principle Study to Investigate the SAFETY and Efficacy of Cobimetinib and Atezolizumab in Advanced Rare Tumors
Phase	II
Protocol Version	7
Version Date	3/6/2020
Protocol PI	Kanwal Raghav
Department	GI Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	134104

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1. PROTOCOL SYNOPSIS

TITLE: A Phase II, Open-label, Single-arm, Multi-cohort, Proof-of¬-principle Study to Investigate the Efficacy of Cobimetinib and Atezolizumab in Advanced Rare Tumors.

PROTOCOL NUMBER: MD 2016-0869

VERSION NUMBER: 7

TEST PRODUCT: Cobimetinib (RO5514041); Atezolizumab (RO5541267)

PHASE: IIA

INDICATION: Advanced Rare Tumors

SPONSOR: The University of Texas MD Anderson Cancer Center, Houston, TX

PRINCIPAL INVESTIGATOR: Kanwal Raghav, MD

Objectives & Endpoints

1. **Primary:**
   - To evaluate the efficacy of cobimetinib plus atezolizumab (COTEZO) in cohorts of advanced rare tumors using objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
2. **Secondary Objectives:**
   - **Efficacy Objectives:**
     - To determine objective response rate (ORR) per immune-related RECIST criteria (irRECIST).
     - To determine progression-free survival (PFS) on COTEZO per RECIST and irRECIST.
     - To determine overall survival (OS) on COTEZO in cohorts of advanced rare tumors.
     - To determine disease control rate (DCR) and duration of response (DOR) on COTEZO per RECIST and irRECIST.
   - **Safety Objectives:**
     - To determine safety profile and adverse events encountered by patients with advanced rare tumors treated with COTEZO.
   - **Translational Objectives:**
     - To collect and bank tumor tissue and peripheral blood for future correlative analyses from patients with advanced rare tumors treated with COTEZO.

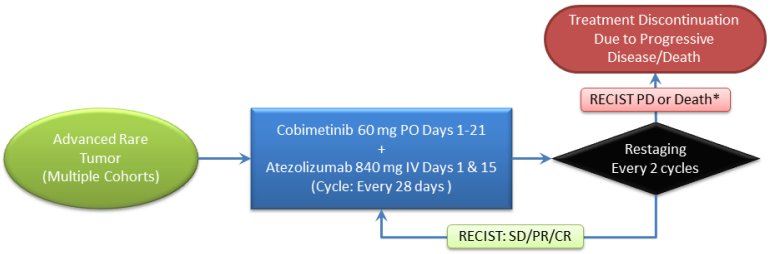
Study Design

This study will be a single-arm, open-label, non-randomized trial evaluating the combination of cobimetinib, a highly selective oral reversible inhibitor of MEK1 and MEK2, and atezolizumab, a fully humanized monoclonal programmed cell death ligand 1 (PD-L1) antibody, in multiple cohorts of patients with advanced rare tumors. After signing informed consent, all eligible patients will be treated with a combination of cobimetinib and atezolizumab (See Study schema). The primary

objective is to assess the efficacy of this combination as measured by ORR using RECIST v1.1. Patients will need to sign a separate treatment beyond progression consent in such cases.

Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy (especially during the flare time-window of the first 12 weeks of treatment to account for expected delayed response). In such cases confirmation of progression is recommended minimum 4 weeks after the first immune-related PD assessment. Such subjects must discontinue therapy when further progression is documented.

Figure: Study Schema



Abbreviation: CR, complete response; IV, intravenous; mg, milligram; PD, progressive disease; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors v1.1; SD, stable disease. * Treatment beyond initial RECIST PD can be considered in subjects experiencing clinical benefit and tolerating study therapy. In such cases confirmation of PD is recommended minimum 4 weeks after the first immune-related PD assessment. Such subjects will discontinue therapy when further progression is documented.

Sample size and anticipated duration	**Targeted enrollment**	**Accrual Duration (months)**	**Follow-up Duration (months)**
Appendiceal adenocarcinoma	20	18	12
Cutaneous squamous cell carcinoma	20	18	12
Small bowel adenocarcinoma	20	18	12
Total	60		

Eligibility Criteria:

INCLUSIONS:

For individual baskets:

- **Appendiceal Adenocarcinoma**
  - Not considered candidate for curative surgery.
- **Cutaneous squamous cell carcinoma**
  - Patients with either metastatic or locally advanced cutaneous squamous cell carcinoma that are technically resectable but in whom surgery is expected to lead to substantial function impairment or disfigurement are eligible.
- **Small bowel adenocarcinoma**

- Must be refractory or intolerant to at least one line of 5FU-based chemotherapy for metastatic disease.

General Inclusion Criteria:

1. Must have histologically or cytologically documented rare tumor as defined per protocol that is metastatic or locally advanced and unresectable.
2. Must be refractory or intolerant to standard lines of therapy.
3. Presence of radiographically evaluable disease.
4. Must have completed prior chemotherapy, immunotherapy, or radiation therapy at least 14 days prior to start of treatment and all toxicity must be resolved to CTCAE v4.0 Grade 1 (with the exception of CTCAE v4.0 Grade 2 neuropathy) prior to start of treatment.
5. ECOG Performance Status of 0-2.
6. Age ≥ 18 years.
7. Tissue Parameters:
    a. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 4 unstained slides, with an associated pathology report, for testing of tumor PD-L1 expression (Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable).
    b. Tumor tissue should be of good quality based on total and viable tumor content. Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
    c. Patients who do not have tissue specimens meeting eligibility requirements must be willing to undergo a biopsy during the screening period.
8. Must have adequate hematologic function as evidenced by all of the following within 14 days prior to enrollment: ANC ≥ 1,000/mcL; platelets ≥ 75,000/mcL; and hemoglobin ≥ 9 g/dL.
9. Must have adequate hepatic function as evidenced by all of the following within 14 days prior to enrollment: AST, ALT, and ALP ≤ 3 x institutional upper limit of normal (IULN) without liver mets or ≤ 5 x IULN with liver metastases; and bilirubin ≤ 1.5 mg/dL.
10. Must have adequate kidney function as evidenced by calculated creatinine clearance > 30 ml/min within 14 days prior to enrollment.
11. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
12. Patients must be informed of investigational nature of this study and must be willing to give written informed consent in accordance with institutional and federal guidelines. Patients must be able to comply with the requirements and assessments of the study protocol.

EXCLUSIONS:

For individual baskets:

- **Appendiceal Adenocarcinoma**
  - Must not have clinically symptomatic malignant bowel obstruction.
- **Cutaneous squamous cell carcinoma**
  - None
- **Small bowel adenocarcinoma**
  - Must not have clinically symptomatic malignant small bowel obstruction.

General Exclusion Criteria:

1. Presence of Brain metastases (unless they have been adequately treated with radiotherapy or surgery and stable for at least 30 days prior to enrollment provided patient is neurologically asymptomatic and without corticosteroid treatment for at least 7 days prior to enrollment).
2. Uncontrolled intercurrent illness including, but not limited to diabetes, hypertension, severe infection, severe malnutrition, unstable angina, Class II-IV New York Heart Association (NYHA) congestive heart failure (see Section 18.1), ventricular arrhythmias, active ischemic heart disease, or myocardial infarction within 6 months prior to enrollment.
3. 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.
4. Patients will be excluded from study participation if they currently are known to have any of the following risk factors for RVO:
   a. Glaucoma with intraocular pressure ≥ 21 mmHg
   b. Grade ≥ 2 serum cholesterol
   c. Grade ≥ 2 hypertriglyceridemia
   d. Grade ≥ 2 or symptomatic hyperglycemia (fasting)
   e. Grade ≥ 2 uncontrolled hypertension (patients with a history of hypertension controlled with anti-hypertensive medication to Grade ≤ 1 are eligible
5. Active malignancy (other than CRC) or a history of prior malignancy within the past 3 years. Adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, ductal carcinoma in situ, other low grade lesions such as incidental appendix carcinoid or any other cancer from which the patient has been disease and treatment free for two years are allowed. Prostate cancer patients on active surveillance are eligible.
6. Pregnant or nursing patients due to risk of fetal or nursing infant harm. Women/men of reproductive potential who do not agree to use an effective contraceptive method while on study and for at least 6 months after study treatment.
7. Exclusion criteria related to study medication (any cancer immunotherapy including CD137 agonists, anti−PD-1, anti−PD-L1, or anti-CTLA4 or any MEK or ERK inhibitor).
8. Left ventricular ejection fraction (LVEF) < institutional lower limit of normal or < 50%.
9. History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome,

Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis

a. Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

b. Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.

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

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

ii. Rash must cover less than 10% of body surface area (BSA)

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

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

10. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

    a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

11. History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection.

    a. Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.

    b. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

12. Active tuberculosis or severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

13. Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN] or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1.

14. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

15. Prior allogeneic bone marrow transplantation or prior solid organ transplantation.

Study Methodology

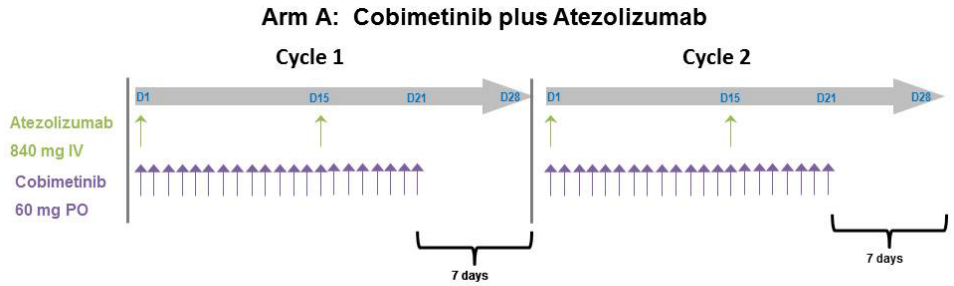
After signing informed consent, patients will undergo screening procedures that include laboratory tests (e.g., hematology, chemistries, liver function tests); left-ventricular function evaluation (echocardiogram [ECHO]); contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis; and ophthalmologic (if clinically indicated) assessments. All eligible patients will be enrolled and treated with cobimetinib plus

atezolizumab and closely monitored for safety and tolerability during all cycles of therapy, at the end-of-study treatment visit, and during the follow-up period. The NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatments on all patients. Tumor response will be evaluated according to RECIST v1.1 and immune-related RECIST (irRECIST). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation by investigators at 8-week intervals. Treatment will continue until the patient has disease progression according to RECIST v1.1 or irRECIST, unacceptable toxicity, death, patient or physician decision to withdraw, whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. All patients will be followed for survival unless consent is withdrawn. Patients will undergo mandatory biopsy prior to cycle 2 for evaluation of immune infiltration and at progression. Archival tissue will be collected for biomarker analysis and MSI-testing will be performed for patients with small bowel and appendiceal adenocarcinoma.

Treatment Plan:

All patients on the study will be enrolled and receive Cobimetinib 60 mg orally on Days 1−21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle.

Figure: Treatment Schedule



Statistical Methods

The primary endpoint is best ORR (PR or CR) measured as per RECIST 1.1. Three parallel single-stage phase II trials will be conducted. A total of 60 patients will be enrolled, i.e., 20 patients in each tumor group. Considering the rareness of the disease, the patient accrual rate is approximately 1 to 2 patients per month per tumor group.

Sample size calculation

For each tumor group, we will estimate the best ORR and its exact confidence interval (CI). When the sample size is 20, and the response rate is 0.3, the two-sided 95% exact CI using the Clopper and Pearson method will be (0.119, 0.543).

For each tumor group, we will also compare its overall best response rate to the historical control based on the current literature. Let p represent the overall best response rate, we will perform independent Binomial test against H0: p=0.1 for each group, with a 1-sided type I error rate of 0.05. The sample size of 20 will provide 76% power to detect an improved best ORR being 30% compared to 10%.

Safety Analysis

The safety analyses will include all treated patients who received at least one dose of study treatment. Toxicity data will be summarized by frequency tables for each tumor type group.

2. INTRODUCTION

2.1 RATIONALE FOR MULTI-COHORT CLINICAL TRIAL IN RARE TUMORS

Major research efforts have led to therapeutic advances in common cancers and improved survival for these cancer patients.**(Kris et al., 2010)** However, rare cancers have been less well studied in clinical research setting and treatment options for these patients are less evolved. As a result, treatments are often based on inadequate or minimal evidence and survival in patients with rare cancers remains poor. Developing novel therapeutics in this space is a large unmet need.**(Casali et al., 2015)** Rare cancers are defined as cancers with prevalence of < 64 and < 50 per 100,000 people in the United States and European Union, respectively.**(Gagne et al., 2014)** Although, conducting clinical research for rare cancers is riddled with multiple challenges including feasibility of accrual and lack of clinical expertise, we feel that with our clinical enterprise around diverse orphan tumors, we can overcome these challenges. This collaborative umbrella effort with Genentech is an effort towards facilitating development of novel therapeutic strategies in multiple rare tumors to improve outcomes in patients with these orphan cancers.

2.2 THE PROGRAMMED T-CELL DEATH LIGAND-1 PATHWAY

Encouraging clinical data in the field of tumor immunotherapy have demonstrated that therapies that are focused on enhancing T-cell responses against cancer can result in significant survival benefit in patients with Stage IV cancer **(Hodi et al. 2010; Kantoff et al. 2010).** Therefore, immunomodulation represents a promising new strategy for cancer therapy that may result in improved anti-tumor activity.

Programmed T-cell death ligand-1 (PD-L1) expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in some cancers **(Thompson et al. 2006; Hamanishi et al. 2007; Ozaki and Honjo 2007; Hino et al. 2010).** PD-L1 is one of two ligands (PD-L1 and PD-L2) that bind programmed cell death-1 (PD-1). The PD-1 receptor is an inhibitory receptor expressed on T cells following T-cell activation in states of chronic stimulation, such as chronic infection or cancer **(Blank et al. 2005; Keir et al. 2008).** Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity that lead to the functional inactivation of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion **(Blank and Mackensen 2007).** Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor–specific T-cell immunity.

Blockade of PD-L1 or PD-1 with mAbs results in strong and often rapid anti-tumor effects in several mouse tumor models **(Iwai et al. 2002; Strome et al. 2003)** and has demonstrated clinical activity with drugs such as atezolizumab **(Besse et al. 2015; Rosenberg et al. 2015; Vansteenkiste et al. 2015).**

Atezolizumab is a humanized IgG1 mAb that targets PD-L1 and inhibits its interaction with its receptors, PD-1 and B7-1 (also known as CD80). Both of these interactions are reported to provide inhibitory signals to T cells. Atezolizumab was engineered to impair its binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

2.3 THE MAPK SIGNALING PATHWAY AND REGULATION OF THE IMMUNE TUMOR MICROENVIRONMENT

The MAPK signaling cascade is a key intracellular signaling network that transduces multiple proliferative and differentiating signals from the extracellular environment to the nucleus of cells to activate cellular growth and differentiation. Signaling through ERK is one major MAPK pathway that has been identified that plays a significant role in normal cellular regulation **(Johnson and**

Lapadat 2002; Roberts and Der 2007). Given the central role that the MAPK pathway plays in normal cellular development, abnormal regulation of this signaling pathway could lead to tumorigenesis through contribution to uncontrolled proliferation, invasion, metastasis, and angiogenesis as well as diminished apoptosis.

The MAPK pathway has also been implicated in the regulation of the immune microenvironment of tumors. In in vitro cell lines, blocking the MAPK pathway was shown to increase antigen expression and enhance reactivity to antigen−specific T lymphocytes **(Boni et al. 2010).** In melanoma patients who are treated with a combined BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi), increased intratumoral lymphocytes (CD4- and CD8-positve T cells) were observed compared to pre-treatment biopsy samples **(Kakavand et al. 2015)**. Furthermore, pre-treatment biopsies where there were increased tumor-infiltrating lymphocytes demonstrated a larger increase in tumor-infiltrating lymphocytes and PD-1 expression after treatment with a BRAFi and MEKi **(Cooper et al. 2015; Kakavand et al. 2015; Liu et al. 2015)**. The inhibition of the MAPK pathway leads to an increase in immune effector cells in the tumor, thus priming the microenvironment to enable to immune system to attack the tumor.

Inhibition of the MAPK pathway has focused on the suppression of targets within this signaling network, such as MEK1 and MEK2. There are multiple upstream activating signals, but multiple alternative pathways exist to bypass their inhibition and still activate ERK1 and ERK2. ERK1 and ERK2 can only be activated and phosphorylated by MEK1 and MEK2, which therefore render MEK1 and MEK2 as key signaling hubs for the inhibition of the MAPK pathway.

Cobimetinib is an orally dosed, potent and highly selective inhibitor of MEK.

2.4 BACKGROUND ON ATEZOLIZUMAB MONOTHERAPY

See the Atezolizumab Investigator's Brochure for additional details on nonclinical and clinical studies (See Supplementary Material).

2.4.1 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetics, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, pharmacokinetic (PK), and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Based on the similar binding affinity and pharmacologic activity of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down modulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

2.4.2 Clinical Experience

2.4.2.1 Ongoing Clinical Studies

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

Phase I Study PCD4989g, a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion once every three weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

2.4.2.2 Clinical Safety as a Single Agent

The safety data for atezolizumab have been derived mainly from the treatment of patients in Study PCD4989g. As of 10 May 2015, the clinical database contained preliminary safety data from 558 patients who have received any amount of atezolizumab at doses between 0.01 and 20 mg/kg across multiple tumor types. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) has been established.

Adverse Events

Of the 558 treated patients, 520 (93.2%) reported an adverse event regardless of attribution to atezolizumab. The majority of these adverse events were Grade 1 or 2 in maximum severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The most frequently observed adverse events (occurring in $\geqslant$ 10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema.

There were 66 patients (11.8%) who experienced Grade ≥ 3 adverse events that were assessed as related to study drug by the investigators. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased γ-glutamyl transferase, lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

Immune–Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune–mediated adverse events have been closely monitored during atezolizumab clinical program. These include potential dermatologic, hepatic, gastrointestinal, endocrine, neurologic, and respiratory events as well as events of hepatitis/elevated liver function tests and influenza-like illness that are considered potential adverse drug reactions associated with atezolizumab.

Refer to the atezolizumab Investigator's Brochure for details regarding immune–mediated adverse events and identified risks (adverse drug reactions) observed in patients treated with atezolizumab as well as recommended management guidelines for atezolizumab-specific immune–mediated adverse events.

2.4.2.3 Clinical Activity

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)–based responses (i.e., RECIST v1.1 responses), have been observed in patients with different tumor types, including non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, bladder cancer, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma treated with atezolizumab monotherapy in Study PCD4989g.

Analyses of PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g, with results suggesting that PD-L1 expression is likely to be associated with response to atezolizumab.

Among 345 efficacy evaluable patients treated as of 21 October 2013 (data cutoff of 21 April 2014), with a median of 30.4 weeks of follow-up, 62 patients experienced objective responses per RECIST v1.1, with an overall response rate (ORR) of 18% (95% CI: 14.1%, 22.3%). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The atezolizumab—F. Hoffmann-La Roche Ltd 29/Protocol GO30140, Version 1 median duration of response (DOR) was 77.6 weeks (range: 6.4 + to 97.9 + weeks, for which the "+" denotes a censored value). The majority of these responses have been durable, with 72.6% of responses (45 of 62 patients) ongoing as of the clinical cutoff date.

2.4.2.4 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1- and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution at steady state ranged from 3.20 to 4.44 mL/day/kg and 48.1–65.7 mL/kg, respectively, which is consistent with the expected pharmacokinetics of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients of all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses ranging from 10–20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

2.5 BACKGROUND ON COBIMETINIB MONOTHERAPY

Cobimetinib is a reversible, potent, and highly selective inhibitor of MEK1 and MEK2. Cobimetinib is approved in the United States, European Union, Switzerland, and in multiple other countries across the world for use with vemurafenib for the treatment of advanced BRAF-mutated melanoma. See the Cobimetinib Investigator's Brochure for additional details on nonclinical and clinical studies (See Supplementary Material).

2.5.1 Summary of Nonclinical Studies

Cobimetinib inhibits proliferation of a variety of human tumor cell lines through inhibition of MEK1 and MEK2. In addition, cobimetinib inhibits ERK phosphorylation in xenograft tumor models and stimulates apoptosis. Cobimetinib accumulates in tumor xenografts and remains at high concentrations in the tumor after plasma concentrations have declined. The activity of cobimetinib to inhibit ERK1 phosphorylation is more closely correlated with its concentration in tumor tissue than in plasma; in general, there is a good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models. Tumor regression has been observed in several human tumor xenograft models. This regression was dose dependent with up to 100% regression at the highest doses tested. The models studied included CRC, malignant melanoma, breast carcinoma, and anaplastic lung carcinoma.

A characterization of the pharmacologic and PK properties of cobimetinib was performed in a series of nonclinical studies that are summarized in the cobimetinib Investigator's Brochure.

The nonclinical toxicity of cobimetinib was characterized in single– and repeat–dose general toxicity studies in rats and dogs, in vitro genotoxicity studies, embryolethality/teratogenicity studies in rat, and cardiovascular, neurobehavioral, and respiratory safety pharmacology studies. The studies are summarized in the Cobimetinib Investigator's Brochure.

2.5.2 Clinical Experience

As of October 2015, cobimetinib had been administered alone or with other agents to more than 1000 adult cancer patients and approximately 120 healthy volunteers in 18 clinical trials; the vast majority of patients had been treated with cobimetinib plus other agents, such as vemurafenib. These include one trial of cobimetinib as a single agent seven clinical pharmacology studies, and nine trials of cobimetinib with other agents.

Study MEK4592g was a Phase I, non-randomized, open-label, safety and PK dose-escalation study. The study was conducted in patients with metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. A total of 115 patients were treated, and the study has since been completed.

The study consisted of five treatment stages:

- Stage I: Dose-escalation cohorts; patients were treated on a 21-days-on, 7-days-off (21/7) schedule to determine the MTD.
- Stage IA: Dose-escalation cohorts; patients were treated on a 14-days-on, 14-days-off (14/14) schedule to determine the MTD on an alternate dosing regimen.
- Stage II: Expansion cohort with the MTD determined in Stage I (60 mg daily [QD] 21/7) in patients harboring a BRAF, NRAS, or KRAS mutation.
- Stage IIA: Expansion cohort with the MTD determined in Stage IA (100 mg QD 14/14) in patients harboring a BRAF, NRAS, or KRAS mutation.
- Stage III: A dedicated drug-drug interaction study at the MTD determined in Stage I (60 mg QD 21/7) in approximately 20 patients with solid tumors.

2.5.2.1 Dose-Limiting Toxicities

Four DLTs were observed in Stage I (21/7 dosing schedule) of Study MEK4592g. At the 40-mg dose level, a DLT of Grade 4 hepatic encephalopathy and Grade 3 elevated ammonia was reported in a patient with pre-existing liver metastases. At the 60-mg dose level, a DLT of Grade 3 rash was reported that improved with skin toxicity management and drug holiday. At the 80-mg dose level, two DLTs were reported: 1 patient with Grade 3 diarrhea despite treatment with anti-diarrheal medications and 1 patient with Grade 3 rash.Two DLTs were observed in Stage IA (14/14 dosing schedule), both at the 125-mg dose level. One patient had Grade 3 rash and another had Grade 3 blurred vision associated with neurosensory detachment of the retina.

Adverse Events

All patients in Study MEK4592g experienced an adverse event. The most frequent adverse events were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea and vomiting (33.9% each), and edema peripheral (28.7%). Other events that occurred in ≥ 10% of patients included anemia, abdominal pain, constipation, hypokalemia, decreased appetite, headache, dizziness, back pain, increased AST, dermatitis acneiform, pruritus, and dry skin. Among the patients who received cobimetinib 60 mg 21/7, the most frequent treatment−emergent adverse events were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea and edema peripheral (31.1% each), and vomiting (28.9%).

Grade≥ 3 Adverse Events

Among all cobimetinib-treated patients, 5 patients (4.3%) experienced a Grade 4 adverse event, and 53 patients (46.1%) experienced a Grade 3 adverse event. The most frequent Grade 3 and Grade 4 adverse events were hyponatremia (9.6%), fatigue (8.7%), anemia (7.8%), and diarrhea and hypokalemia (6.1% each).

Serious Adverse Events

A total of 49 patients (42.6%) experienced a serious adverse event. The most common types of serious adverse events were gastrointestinal disorders (n = 17), but there were no trends in specific preferred terms. The gastrointestinal serious adverse events, such as intestinal obstructions and gastrointestinal hemorrhages, occurred in patients with gastrointestinal malignancies. Serious adverse events reported for more than 2 patients among all patients in the study were anemia, bile duct obstruction, dehydration, syncope, and respiratory arrest (3 patients each [2.6%]).

2.5.2.2 Efficacy

Best overall response (BOR) was assessed for 74 of 97 patients in Stages I, IA, II, and IIA. Overall 6 patients (all of whom had melanoma; 6.2%) had a confirmed partial response (PR), 28 patients (28.9%) had stable disease (SD), and 40 patients (41.2%) had progressive disease. Out of the 14 CRC patients, all patients experienced progressive disease. In Stage III of Study MEK4592g, 18 patients were accrued and BOR was assessed for 14 of 18 patients. Four patients (22.2%) had SD as their BOR, and 2 patients (11.1%) had unconfirmed tumor responses.

2.6 COMBINED INHIBITION OF PD-L1 AND MAPK SIGNALING PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

Several clinical studies have tested checkpoint inhibitors in MSI-Stable metastatic colorectal cancer with disappointing results **(Brahmer et al. 2012; Topalian et al. 2012; Poulin-Costello et al. 2013)**. One potential mechanism to convert otherwise resistant cancers is to recruit immune cells to the tumor sites so that the anti-PD L1 can be effective in activating the local immune system against the cancer cells. Nonclinical models suggest that MEK inhibition may have pleiotropic effects that could impact the tumor immune microenvironment, as the MAPK pathway has been implicated in the immune resistance of tumors and inhibition of this pathway can lead to increase CD8−positive T-cell infiltration **(Kakavand et al. 2015; Liu et al. 2015).**

Within the tumor, MEK inhibition results in increased major histocompatibility complex (MHC) class I expression and tumor antigen presentation, which acts to enhance tumor recognition by the immune system. Interestingly, MEK inhibition in tumors also increases expression of the checkpoint receptor PD-L1, which could counteract the increased presentation of tumor antigens. Lastly, the MAPK pathway is known to regulate a number of cytokines and chemokines, such as VEGF, interleukin (IL)-6 (IL-6), IL-8, and granulocyte−macrophage colony-stimulating factor, which may impact recruitment of vascular and other stromal cell types, including myeloid−derived suppressive cells (MDSCs) that can inhibit the anti-tumor activity of T cells **(Bancroft et al. 2001; Sano et al. 2001; Bancroft et al. 2002; Phan et al. 2013).** Activity of MEK inhibition outside of the tumor cells may further contribute to the modulation of the immune microenvironment that could enable a more permissive immune reaction against the tumor. These effects include inhibition of tumor vascular maturity and integrity, tumor infiltration, activity of MDSCs, neutrophils, increased activity of antigen-presentation cells, such as macrophage and dendritic cells, and recruitment and activation status of T-cell subsets, including CD8-positive cytolytic and CD4−positive helper cells **(Giordano et al. 2015; Liu et al. 2015; Loi et al. 2015).**

Collectively, these effects enable tumors to demonstrate stronger anti-tumor responses with the combination of a MEKi and PD-L1/PD-1 blockade in multiple mouse models, including colorectal, breast, and melanoma models **(Liu et al. 2015; Loi et al. 2015).** Increased anti-tumor activity is associated with increased CD8−positive T-cell infiltration of tumors that express markers consistent with tumor−cell cytolytic activity. These data suggest that MEK inhibition can modulate the tumor immune microenvironment and enable better tumor recognition and killing by the immune system, particularly when paired with a checkpoint inhibitor against the PD-1/PD-L1 axis.

2.6.1 Rationale of the Combination

Targeting immune checkpoint such as programmed cell death protein 1 (PD1) and programmed cell death 1 ligand 1 (PDL1) has led to striking benefit in numerous cancers by blocking immunoinhibitory signals and enabling an effective antitumour response. **(Pardoll, 2012)** Atezolizumab is an engineered humanized immunoglobulin G1 monoclonal antibody that binds selectively to programmed death ligand 1 (PD-L1) and inhibits the immune checkpoint PD-1/PD-L1 pathway. Atezolizumab has shown encouraging activity in metastatic urothelial carcinoma and non-small cell lung cancer (NSCLC) in two pivotal studies. **(Fehrenbacher et al., 2016; Rosenberg et al., 2016)** Although, anti-PD1/PD-L1 therapy works for some select tumors, many tumors are resistant to these agents due to presence of immune evasive mechanisms in tumors and their microenvironment. The Mitogen-activated Protein Kinase (MAPK) signaling cascade is a key network involved in tumor proliferation, growth and differentiation. Recently, emerging data has implicated MAPK signaling in the regulation of immune microenvironment of tumors. In preclinical models, blocking the MAPK pathway increases antigen expression, enhances reactivity to antigen−specific T lymphocytes, increases intratumoral lymphocytes, and enhances anti-PDL1 activity.**(Kakavand et al., 2015)** Synergistic combination of MEK inhibitor with PD-1 and PD-L1 targeting is more efficacious than any single agent and increases tumor-infiltrating CD8 (+) T cells.**(Liu et al., 2015)** Furthermore, MEK inhibitors have shown to enhance host antitumor immunity by improving T cell infiltration and function, and may serve to prime the tumor microenvironment for response to checkpoint inhibitors. **(Ebert et al., 2016)** The inhibition of the MAPK pathway leads to an increase in immune effector cells in the tumor, thus priming the microenvironment to enable the immune system to attack the tumor, thereby making resistant tumors sensitive to immune inhibition.

A Phase Ib study of COTEZO in patients with mismatch repair-proficient, an otherwise resistant tumor type with regards to anti-PD therapy, advanced colorectal cancer (N = 23) showed an ORR of 17% (4 PR, 5 SD).**(Bendell JC, 2016)** The combination was well tolerated at the maximum administered doses.

2.7 CLINICAL DATA OF COBIMETINIB PLUS ATEZOLIZUMAB – STUDY GP28363

Study GP28363 is a Phase Ib, open-label, multicenter study designed to assess the safety, tolerability, and pharmacokinetics of cobimetinib plus atezolizumab in patients with advanced solid tumors. The study has two stages: Stage 1 (dose escalation) and Stage 2 (expansion). Stage 1 is designed to establish the combination MTD for cobimetinib plus atezolizumab. In Stage 2, the recommended Phase II dose and schedule were investigated in tumor−specific expansion cohorts: KRAS-mutant mCRC, NSCLC, and metastatic melanoma.

In the Stage 1 dose−escalation phase, there were no DLTs, and 60 mg cobimetinib 21/7 with 800 mg atezolizumab every 2 weeks (q2w) was determined to be the recommended Phase II dose. As of 12 October 2015, a total of 90 patients were accrued and evaluable for safety. The most common adverse events reported were diarrhea (71.1%), fatigue (55.6%), nausea (41.1%), rash (41.1%), vomiting (38.9%), decreased appetite (37.8%), constipation (35.6%), pruritis (32.2%), dermatitis acneiform (28.9%), and blood CPK increased (25.6%). The most common Grade 3 or higher adverse events reported were anemia (10.0%), diarrhea (7.8%), fatigue (7.8%), dyspnea (6.7%), rash (4.4%), and blood CPK increased (4.4%).

Nine patients experienced Grade 5 (fatal) adverse events. These included disease progression in 3 patients and large intestine perforation, asthenia, dyspnea, pneumonia, sepsis, and road traffic accident in 1 patient each. The safety of cobimetinib plus atezolizumab appeared similar to the known single−agent safety profiles of each drug; no new safety signals were noted.

In the expansion cohort for mCRC patients with KRAS−mutation (n = 23); 4 patients had a PR, 5 had SD, and 14 had progressive disease. All the patients who responded had MSI-stable tumors. Furthermore, biomarker evaluation from the serial tumor biopsy cohort showed a 4-fold increase of CD8−positive T-cell infiltration in 75% of tumors as well as increases in PD-L1 and MHC-I expression, which supports the hypothesis that this use of cobimetinib and atezolizumab has beneficial immunomodulatory effects at the tumor site that allow for immune anti−tumor activity.

2.8 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The combination of a MEKi and PD-L1 inhibitor has nonclinical and clinical data that strongly support further evaluation in previously treated mCRC patients and other tumor types. Both in vitro and in vivo models have shown that the MAPK pathway plays an important role in the immune tumor microenvironment, and MEK inhibition leads to increases in MHC-1 and PD-L1 expression as well as increases in CD8−positive lymphocyte recruitment into the tumor microenvironment. This enhancement of the local immune system in combination with a PD-L1 inhibitor has demonstrated increased efficacy in nonclinical and clinical models. The Phase Ib clinical trial evaluating cobimetinib plus atezolizumab in previously treated KRAS−mutated mCRC patients shows an efficacy of a 13% PR rate and a 26% SD rate, with some responses lasting more than 1 year. The regimen is well tolerated, and the safety profile is manageable and tolerable.

2.9 DISEASE SPECIFIC RATIONALE

2.9.1 Appendiceal Adenocarcinoma

Appendiceal tumors are rare with an age-adjusted incidence of 0.12 cases per 1,000,000 per year. **(McCusker et al., 2002)** Metastatic appendiceal adenocarcinomas are tumors characterized by a relatively indolent natural clinical course if low-grade and very aggressive biology if high grade. **(Asare et al., 2016; Carr et al., 2016)** Even though cytoreductive surgery (CRS) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard therapy and results in prolonged survival in low-grade tumors, high tumor burden and medical comorbidities can exclude patients from curative intent surgery. **(Smeenk et al., 2007)** In high-grade tumors, chemotherapy is the only effective option but has limited benefit and chemotherapy in low-grade cases has shown no or little clinical benefit. **(Asare et al., 2016)** There exists an unmet need for active targeted agents in this setting. Emerging data has shown a higher frequency of KRAS mutations in low-grade appendiceal neoplasms (70%-80%) compared to high-grade tumors. **(Alakus et al., 2014; Raghav et al., 2013)** Pre-clinical data has shown that MAPK signaling pathway is upregulated in these tumors and MAPK inhibition (RDEA119) resulted in inhibition of mucinous tumor growth and prolongation of survival in xenograft models. **(Dilly et al., 2015)** In clinical setting, Selumetinib, another MAPK inhibitor, has shown promising activity in recurrent ovarian/peritoneal low-grade serous carcinoma, a tumor type which shares many features (peritoneal carcinomatosis, indolent biology, chemo-resistance, KRAS mutations etc.) with low-grade appendiceal adenocarcinomas. **(Farley et al., 2013)** Cobimetinib (Cobi) is an orally active, highly selective MEK1/2 (MAPK) inhibitor that has shown anti-tumor activity in RAS mutant xenografts. **(Garnock-Jones, 2015)** Appendiceal adenocarcinomas share many commonalities with metastatic colorectal cancer (mCRC) and is often treated as such. COTEZO is being actively investigated in a randomized phase III study in mCRC. Based on this preliminary information, we propose a proof-of-principle to explore activity of COTEZO in appendiceal adenocarcinomas.

2.9.2 Cutaneous Squamous Cell Carcinoma

Although cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy in the US, with an incidence of approximately 200,000 to 400,000 individuals per year, majority of patients are cured with surgical excision and mortality rate is low (approx. 6,000 deaths yearly).

(Karia et al., 2013; Rees et al., 2015) Rarely, in approximately 3% cases, disease presents with inoperable locally advanced, recurrent, or metastatic disease, for which therapeutic options are limited. There is limited data on the role of systemic therapy in the treatment of recurrent or metastatic cSCC. The main systemic therapy options with activity reported in small prospective studies and retrospective series are cisplatin, 5-FU, and EGFR inhibitors. **(Bichakjian, 2015; Foote et al., 2014; Maubec et al., 2011; Sadek et al., 1990)** Immunotherapy, particularly anti-PD1/PD-L1, has shown activity in a wide range of solid tumors. Evidence shows that mutational burden may correlate with response to immunotherapy. (**Alexandrov et al., 2013; Rizvi et al., 2015)** Work from our group has shown that cSCC is highly mutated, even to an extent greater than melanoma and lung SCC. **(Pickering et al., 2014)** In addition to high-mutational burden, cSCC has several other clinical and biological factors that suggest that it is appropriate for the clinical study of checkpoint inhibitors including the presence of tumor-infiltrating lymphocytes (TILs) **(Freeman et al., 2014; Muhleisen et al., 2009)**, immunosuppression as a risk factor **(Euvrard et al., 2003)**, evidence of direct immunosuppressive effects of UV radiation **(Yu et al., 2014)**, and some clinical efficacy with interferon α-based treatment. **(Lippman et al., 1992)** Approximately 20% of aggressive cSCC also have NRAS mutation. **(Pickering et al., 2014)** Taken together, COTEZO is a rational combination in advanced cSCC.

2.9.3 Small Bowel Adenocarcinomas

Small bowel adenocarcinomas (SBAs) are rare tumors and include one-third of all small bowel cancers, with an estimated 3,250 new cases diagnosed in the USA in 2013. Age-adjusted incidence rates of SBAs is highest among black (14.1 per 1,000,000) followed by white individuals (7.7 per 1,000,000). **(Raghav and Overman, 2013)** Owing to their rarity, anatomical proximity and some similarities to the large bowel, SBAs have frequently been grouped and treated as mCRC. **(Raghav and Overman, 2013)** Mutations in KRAS (codon 12 and 13) have been observed in 40–60% of all sporadic SBAs and this rate is comparable to that seen for CRC. Based on frequent KRAS mutations that occur in small bowel cancers, the RAS/RAF/MAPK pathway seems to have a role in small bowel carcinogenesis. Systemic chemotherapy has been regarded as the mainstay of treatment for patients with metastatic SBAs but to date no randomized trials have been done. Although, multiple agents have demonstrated activity in patients with metastatic SBAs, including 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, gemcitabine and irinotecan with varying response rates, the overall survival remains poor. **(Raghav and Overman, 2013)** Exploring activity of immunotherapy, specifically in combination with immunomodulators is an area of great unmet need for this rare tumor. Initial success of COTEZO in refractory mCRC is encouraging and argues for exploring the combination in SBAs.

2.9.4 Study Hypothesis

Development of immunotherapy in rare tumors is a significant unmet need owing to limited therapeutic options in these tumors and lack of inclusion of these tumors in clinical trials.

Based on preliminary data, we hypothesize that combination therapy with COTEZO will be well tolerated in patients with rare tumors and will have promising and significant anti-tumor activity resulting in improved outcomes. Furthermore, we will be able to create a tissue biorepository of these rare tumors for future correlative studies. We believe that this study is an innovative accelerated pilot effort to assess therapeutic efficacy of COTEZO in multiple rare tumors.

3. OBJECTIVES

This study will evaluate the efficacy and safety of cobimetinib plus atezolizumab in patients with advanced rare tumors.

3.1 PRIMARY OBJECTIVE

- To evaluate the efficacy of cobimetinib plus atezolizumab (COTEZO) in cohorts of advanced rare tumors using objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

3.2 SECONDARY OBJECTIVES

- Efficacy Objectives:
    - **a.** To determine progression-free survival (PFS) on COTEZO in cohorts of advanced rare tumors per RECIST v1.1 and irRECIST.
    - **b.** To determine overall survival (OS) on COTEZO in cohorts of advanced rare tumors.
    - **c.** To determine disease control rate (DCR) and duration of response (DOR) on COTEZO in cohorts of advanced rare tumors per RECIST v1.1 and irRECIST.
    - **d.** To determine objective response rate (ORR) per immune-related RECIST criteria.
- Safety Objectives:
    - **a.** To determine safety profile and adverse events encountered by patients with advanced rare tumors treated with COTEZO.
- Translational Objectives:
    - **a.** To collect and bank tumor tissue and peripheral blood for future correlative analyses from patients with advanced rare tumors treated with COTEZO.

4. STUDY DESIGN

4.1 DESCRIPTION OF THE STUDY

This study will be a single-arm, open-label, non-randomized trial evaluating the combination of cobimetinib, a highly selective, oral, reversible inhibitor of MEK1 and MEK2, and atezolizumab, a fully humanized monoclonal programmed cell death ligand 1 (PD-L1) antibody, in multiple cohorts of patients with advanced rare tumors. After signing informed consent, all eligible patients will be treated with a combination of cobimetinib and atezolizumab (See Study schema). The primary objective is to assess the efficacy of this combination as measured by ORR using RECIST v1.1.

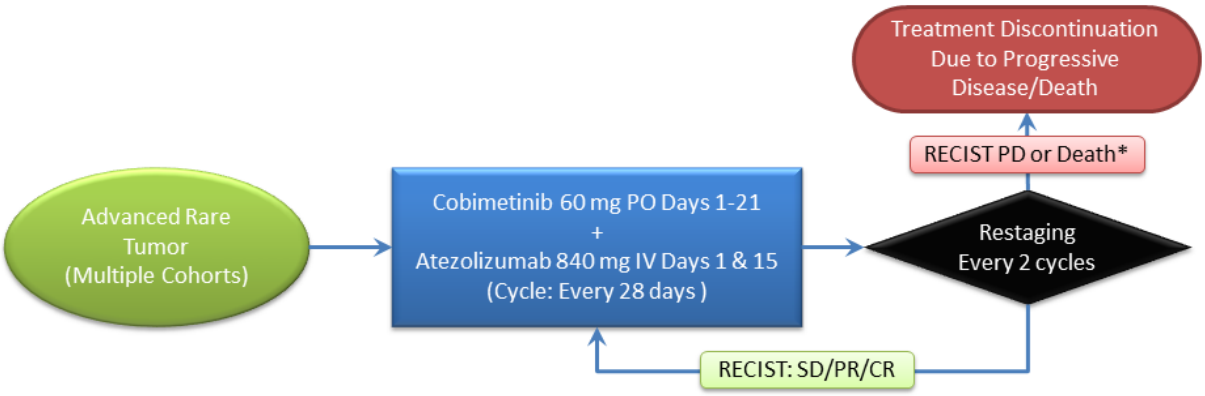
Tumor response will be evaluated according to RECIST v1.1 (see Appendix 6). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Investigators will assess tumor response at 8 week intervals, regardless of any dose delays or treatment cycle. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy (especially during the flare time-window of the first 12 weeks of treatment to account for expected delayed response). In such cases confirmation of progression is recommended minimum 4 weeks after the first immune-related PD assessment. Such subjects must discontinue therapy when further progression is documented.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. The NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatments on all patients.

After discontinuation of study treatment, patients may receive any subsequent line therapy as directed by their treating physician.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

Figure 1: Study Schema

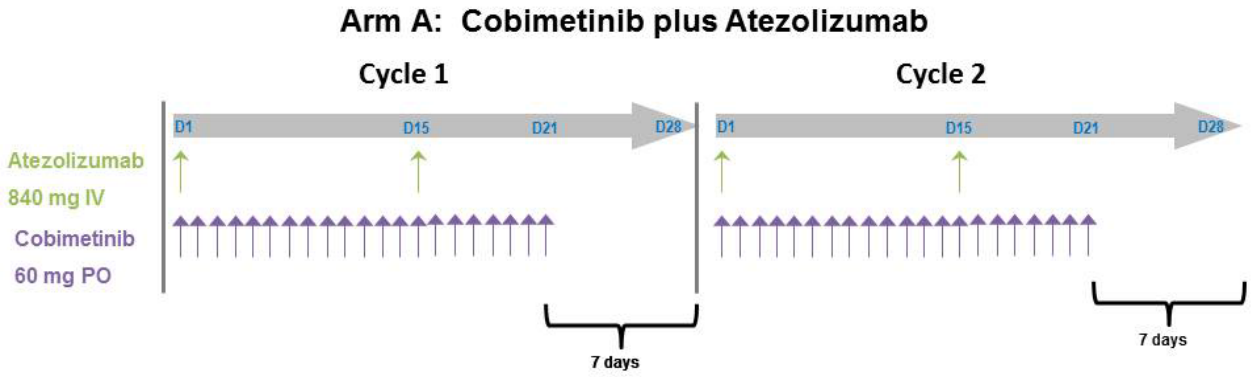


Abbreviation: CR, complete response; IV, intravenous; mg, milligram; PD, progressive disease; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors v1.1; SD, stable disease.

*Treatment beyond initial RECIST PD can be considered in subjects experiencing clinical benefit and tolerating study therapy. In such cases confirmation of PD is recommended minimum 4 weeks after the first immune-related PD assessment. Such subjects will discontinue therapy when further progression is documented.

All patients on the study will be enrolled and receive (Figure 1): Cobimetinib 60 mg orally on Days 1−21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle.

Figure 2: Treatment Schedule



The expected total length of time on study is anticipated to be approximately 15 months, with 2 weeks spent in screening, 4 weeks in washout, 12 months receiving therapy, and 2 months of follow-up prior to the final protocol visit.

Patients will undergo mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by the investigator, prior to cycle 2 days 1 (during week 4) and at the time of first evidence of radiographic disease progression according to RECIST v1.1 within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever

is sooner. These samples will be analyzed to evaluate tumor-infiltrating immune cells [ICs]). In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of cobimetinib and atezolizumab may be analyzed.

4.2 END OF STUDY AND LENGTH OF STUDY

The final analysis will occur after full enrollment, which is expected approximately 18 months after the first patient is enrolled. 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 (i.e., ORR) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 30 months after the first patient is enrolled. In addition, the PI may decide to terminate the study at any time.

4.3 RATIONALE FOR STUDY DESIGN

Study Hypothesis: Combination therapy with COTEZO will be well tolerated in patients with rare tumors and will have significant anti-tumor activity resulting in improved outcomes.

4.3.1 Rationale for Dose and Schedule for Cobimetinib and Atezolizumab

Concomitant administration of atezolizumab and cobimetinib was studied in the Phase Ib Study GP28363. Cobimetinib 60 mg on a 21/7 schedule is the approved dose and schedule of cobimetinib. For administration with cobimetinib, on a 28-day cycle, a dose of 840 mg atezolizumab administered every 2 weeks has the equivalent dose exposure as the 1200 mg every 3 weeks (21–day cycle), the standard dose for the atezolizumab monotherapy. In Study GP28363 atezolizumab was dosed concurrently with cobimetinib at 800 mg IV q2w. The 840 mg dose is expected to be similar to the 800 mg dose of atezolizumab dose and selected in this study to simplify dose administration.

4.3.2 Rationale for the Use of Immune-Modified RECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic progression to be confirmed at a subsequent assessment (see Appendix 5). It is required that radiographic progression is confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression (caused by immune cell infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, use of immune-modified RECIST will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit.

4.3.3 Rationale for Biomarker Assessments

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

Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, after 3 weeks of therapy and at the time of first evidence of radiographic disease progression to evaluate the utility of the biopsy in distinguishing pseudoprogression (caused by immune cell infiltration) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab may be analyzed.

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

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible, tumor tissue collected at 8 weeks of therapy and at the time of progression will enable NGS and RNA profiling to identify germline and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

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

4.3.4 Rationale for Allowing Patients to Continue Treatment until Loss of Clinical Benefit

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents as increase in tumor size does not consistently reflect therapeutic failure **(Wolchok et al. 2009)**. The phenomena of pseudo progression or infiltration of tumor by immune cells may mimic tumor progression. Therefore, as this study is evaluating an immunotherapy, the study will allow patients to continue to receive study treatment after documented RECIST v1.1−defined radiographic disease progression, provided the benefit-risk ratio for the patient remains favorable as assessed by the physician and study monitor (see Section 5.3.3).

In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data.
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease.
- Absence of decline in ECOG Performance Status that can be attributed to disease progression.
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

4.4 OUTCOME MEASURES

4.4.1 Primary Outcome Measure

- ORR (PR or CR) per RECIST v1.1.

4.4.2 Secondary Outcome Measures

- Efficacy Endpoints:
  - **a.** ORR per irRECIST.
  - **b.** PFS per RECIST v1.1 and irRECIST.
  - **c.** OS
  - **d.** DCR per RECIST v1.1 and irRECIST.
  - **e.** DOR per RECIST v1.1 and irRECIST.

4.4.3 Safety Outcome Measures

- Adverse events per CTCAE v4.0.

4.4.4 Translational Outcome Measures

- Tumor tissue and peripheral blood

4.5 SAFETY PLAN

Patients will be evaluated at each study visit for the duration of their participation in the study (see Section 5.6 and Appendix 1).

Please refer to the atezolizumab and cobimetinib Investigator's Brochures for a detailed description of the safety profile of atezolizumab and cobimetinib.

See Section 6 for complete details of the safety evaluation for this study.

4.6 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current US Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

5. MATERIALS AND METHODS

5.1 PATIENT SELECTION

5.1.1 Inclusion Criteria

Patients will be included in the study based on the following criteria:

- Patients must be informed of the investigational nature of this study and must be willing to give written informed consent in accordance with institutional and federal guidelines. Patients must be able to comply with the requirements and assessments of the study protocol.
- Must have histologically or cytologically documented rare tumor as defined per protocol that is metastatic or locally advanced and unresectable. Patients with locally advanced cutaneous squamous cell carcinoma that are technically resectable but in whom surgery is expected to lead to substantial function impairment or disfigurement are eligible.
- Must be refractory or intolerant to standard lines of therapy.
- Must have completed prior chemotherapy, immunotherapy, or radiation therapy at least 14 days prior to start of treatment and all toxicity must be resolved to CTCAE v4.0 Grade 1 (with the exception of CTCAE v4.0 Grade 2 neuropathy) prior to start of treatment.
- Presence of radiographically evaluable disease.
- Age ≥ 18 years

- ECOG performance status ≤2
- Tissue Parameters:
    - ***a.*** Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 4 unstained slides, with an associated pathology report, for testing of tumor PD-L1 expression (Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable).
    - **b.** Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
    - **c.** Patients who do not have tissue specimens meeting eligibility requirements must be willing to undergo a biopsy during the screening period.
- Adequate bone marrow function as indicated by the following as evidenced by all of the following within 14 days:
    - ANC >1000/μL
    - Platelets ≥75,000/μL
    - Hemoglobin >9 g/dL
- Adequate renal function, as evidenced by calculated creatinine clearance > 30 ml/min within 14 days prior to enrollment.
- Must have adequate hepatic function as evidenced by all of the following within 14 days prior to enrollment: AST, ALT, and ALP ≤ 3 x institutional upper limit of normal (IULN) without liver mets or ⩽ 5 x IULN with liver metastases; and bilirubin ⩽ 1.5 mg/dL.
- Able to swallow pills
- Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnancy test if they are either surgically sterile or have been postmenopausal for ≥1 year.
- Fertile men and women must use an effective method of contraception during treatment and for at least 5 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (e.g., implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)
- **For individual baskets:**
    - **Appendiceal Adenocarcinoma**
        - Not considered candidate for curative surgery.
    - **Cutaneous squamous cell carcinoma**

- Patients with either metastatic or locally advanced cutaneous squamous cell carcinoma that are technically resectable but in whom surgery is expected to lead to substantial function impairment or disfigurement are eligible.

- **Small bowel adenocarcinoma**
  - Must be refractory or intolerant to at least one line of 5FU-based chemotherapy for metastatic disease.

5.1.2 Exclusion Criteria

- Presence of Brain metastases (unless they have been adequately treated with radiotherapy or surgery and stable for at least 30 days prior to enrollment provided patient is neurologically asymptomatic and without corticosteroid treatment for at least 7 days prior to enrollment).
- Uncontrolled intercurrent illness including, but not limited to diabetes, hypertension, severe infection, severe malnutrition, unstable angina, Class II-IV New York Heart Association (NYHA) congestive heart failure (see Section 18.1), ventricular arrhythmias, active ischemic heart disease, or myocardial infarction within 6 months prior to enrollment.
- 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 currently are known to have any of the following risk factors for RVO:
  - **a.** Glaucoma with intraocular pressure $\geqslant$ 21 mmHg
  - **b.** Grade $\geqslant$ 2 serum cholesterol
  - **c.** Grade $\geqslant$ 2 hypertriglyceridemia
  - **d.** Grade $\geqslant$ 2 or symptomatic hyperglycemia (fasting)
  - **e.** Grade $\geqslant$ 2 uncontrolled hypertension (patients with a history of hypertension controlled with anti-hypertensive medication to Grade $\leqslant$ 1 are eligible)
- Active malignancy (other than CRC) or a history of prior malignancy within last 3 years. Adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, ductal carcinoma in situ, other low grade lesions such as incidental appendix carcinoid, or any other cancer from which the patient has been disease and treatment free for two years are allowed. Prostate cancer patients on active surveillance are eligible.
- Pregnant or nursing patients due to risk of fetal or nursing infant harm. Women/men of reproductive potential who do not agree to use an effective contraceptive method while on study and for at least 6 months after study treatment.
- Exclusion criteria related to study medication (any cancer immunotherapy including CD137 agonists, anti−PD-1, anti−PD-L1, or anti-CTLA4 or any MEK or ERK inhibitor).
- Left ventricular ejection fraction (LVEF) < institutional lower limit of normal or < 50%.
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's

syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis

a. Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

b. Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.

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

- Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
- Rash must cover less than 10% of body surface area (BSA)
- Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
- No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection.
  a. Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
  b. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis or severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN] or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation.
- **For individual baskets:**
  A. Appendiceal Adenocarcinoma
    - Must not have clinically symptomatic malignant bowel obstruction.
  B. Cutaneous squamous cell carcinoma

- None

C. Small bowel adenocarcinoma

- Must not have clinically symptomatic malignant small bowel obstruction.

5.2 METHOD OF TREATMENT ASSIGNMENT

After written informed consent has been obtained and eligibility established, each patient will be assigned an identification number and enrolled on study and will receive study medications in this single-arm study.

5.3 STUDY TREATMENT

This is a phase IIA, open-label study of cobimetinib and atezolizumab. All patients enrolled on study will receive cobimetinib 60 mg orally on Days 1−21 plus atezolizumab 840 mg IV on Day 1 and Day 15 in a 28-day cycle. For patient who have discontinued cobimetinib, atezolizumab can be given IV at 1680 mg once every 4 weeks.

The Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all atezolizumab and cobimetinib in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

5.3.1 Atezolizumab Dosage, Storage, and Administration

The Atezolizumab is 840 mg drug product will be supplied in a single-use, 15 mL USP/Ph. EUR. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

For more detailed information on drug preparation, storage, and administration, refer to the Investigator's Brochure. Atezolizumab will be supplied by Genentech Inc. The vial is designed to deliver 14 mL (840 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 14 mL volume. The formulation of atezolizumab 840 mg drug product is identical to that of atezolizumab 1200 mg drug product.

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

Table 1: Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
Premedication is allowed.	If patient experienced IRR during any previous infusion, pre-medication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician.
Record vital signs (HR, RR, BP, and T) within 60 min before starting infusion.	Record patient's vital signs (HR, RR, BP, and T) within 60 min before starting infusion.
Infuse atezolizumab (one vial in 250 mL NaCl) over 60 (± 15) min	If the patient tolerated the first infusion well without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) min.

Record vital signs (HR, RR, BP, and T) during the infusion at 15, 30, 45, and 60 min (± 10-min windows are allowed for all timepoints).	If the patient had an IRR during the previous infusion, the subsequent infusion must be delivered over 60 (± 15) min.
Record patient's vital signs (HR, RR, BP, and T) at 30 (± 10) min after the infusion.	Record patient's vital signs (HR, RR, BP, and T) during the infusion if clinically indicated o patient experienced symptoms during the previous infusion.
Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	Record patient's vital signs (HR, RR, BP, and T) at 30 (± 10) min after the infusion, if clinically indicated or patient experienced symptoms during previous infusion. If no reaction occurs, continue subsequent infusions over 30 (± 10) min with same schedule for recording vital signs.

Abbreviations: AE = adverse event; BP = blood pressure; HR = heart rate; IRR = infusion-related reaction; NaCl = sodium chloride; RR = respiratory rate; T = temperature

Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.5, Appendix 7 as well as the atezolizumab Investigator's Brochure. For anaphylaxis precautions, see Appendix 8.

See the Investigator's Brochure for detailed instructions on drug preparation, storage, and administration.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF (See Section 6.3).

Atezolizumab may be prepared, handled, and administered per the current FDA-approved package insert.

5.3.2 Cobimetinib Dosage, Storage, and Administration

The recommended dose for cobimetinib is 60 mg OD for 21 days on, then 7 days off, in a 28 day treatment cycle. The 20 mg cobimetinib drug product is a film-coated, immediate release tablet. The white tablet is round with the engraving "ROCHE" on one side. Tablet imprint is "COB". Cobimetinib will be packaged in blister packs. Cobimetinib should not be stored above 25°C (77°F).

Cobimetinib should be taken once daily at approximately the same time each day and no later than 4 hours after the scheduled time. Cobimetinib can be taken with or without a meal. Cobimetinib tablets should never be chewed, cut, or crushed. At least 7 days off cobimetinib is required prior to starting a new treatment cycle.

Cobimetinib will be supplied by Genentech Inc. as tablets. The 20-mg cobimetinib drug product is a film-coated, white, round, immediate-release tablet. Cobimetinib will be packaged in blister packs. The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. Cobimetinib should not be stored above 25°C (77°F). If the study drug is

stored outside of the permitted temperature ranges, quarantine the affected supply and contact the monitor.

Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Section 5.5 and Appendix 7. For further details, see the cobimetinib Investigator's Brochure.

Cobimetinib may be prepared, handled, and administered per the current FDA-approved package insert.

Cobimetinib compliance will be monitored by study team. Prior to start of each new cycle, patient compliance will be evaluated and documented in eCRF by asking patients about amount of drug consumed and pill counts. Study team will question patients regarding any discrepancies and document the explanation. The returned drug by patient will be documented by study team in eCRF.

5.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab and cobimetinib) will be provided by the Genentech Inc. where required by local health authority regulations. The study site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

Any unused drug will be destroyed according to MDACC's standard operating procedure or will be returned to the Genentech Inc. with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Genentech Inc. The site must obtain written authorization from the Genentech Inc. 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.

5.3.4 Dosing of Study Treatment Beyond Disease Progression

Dosing of study treatment beyond RECIST v1.1−defined disease progression is allowed for patients on all treatment arms. Patients must meet all of the following criteria to be allowed to receive study treatment beyond disease progression:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs indicating unequivocal progression of disease. Patients may continue to receive treatment beyond disease progression in the absence of clinical signs or symptoms of progression despite a rising CEA level.
- No decline in ECOG performance status that can be attributed to disease progression.
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol−allowed medical interventions.
- Patients must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of RECIST v1.1-defined disease progression.
- Approved by the Investigator
- Patients will need to sign a separate treatment beyond progression consent

5.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

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

5.4.1 Permitted Therapy

The following therapies are permitted in the study:

- Hormonal therapy with gonadotropin−releasing hormone agonists or antagonists for prostate cancer
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions. It is not required to withhold atezolizumab during palliative radiotherapy.
- Surgery (preferable) or definitive radiation therapy (with or without radiosensitizing agent) for patients specifically enrolled in the cutaneous squamous cell carcinoma cohort when upfront surgery was considered functionally or cosmetically inappropriate is allowed after a **minimum of two cycles** of therapy with the investigational agents.

- Inactive influenza vaccinations during influenza season ONLY
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drugs. 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.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion−associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and b2-adrenergic agonists).

All medications must be recorded on the Concomitant Medications eCRF.

5.4.2 Therapy Not Permitted

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the anti-cancer agent, and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.

The following medications are prohibited while receiving study treatment, unless otherwise noted:

- Traditional herbal medicines as their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to treatment start date or at any time during the study or within 90 days following the last infusion of atezolizumab.
- For patients on atezolizumab:
    - Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed.
    - Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab
    - Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab
    - Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where 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 (see Section 4.4.2)
- For patients on cobimetinib:
    - Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided as cobimetinib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).
    - Avoid strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

Patients will be given a list of these prohibited medications at the time of consent.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP3A or UGT2B7.

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

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

5.5 STUDY TREATMENT MODIFICATIONS

Guidelines for dose modifications, interruptions, or discontinuations of atezolizumab and/or cobimetinib provided below are not intended to replace the investigator's best clinical judgment with regard to the medical management of her/his individual patients.

5.5.1 Dose Modifications for Cobimetinib

NOTE: Investigators can interrupt dosing of atezolizumab (or cobimetinib) depending on the attribution of the toxicity, which is at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent.

NOTE: If either atezolizumab or cobimetinib are discontinued, dosing with the other drug may continue at the discretion of the investigator.

NOTE: For Grade ⩾ 3 toxicities associated primarily with laboratory abnormalities only, study treatment may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice.

Table 2: Recommended Cobimetinib Dose Modifications

Grade (CTCAE)	Recommended dose modification
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at the same dose of 60 mg QD (3 tablets)
Grade 2 (intolerable) or Grade 3 or 4 (any)*	
First appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 40 mg QD (2 tablets)
Second appearance	Interrupt treatment until Grade ≤ 1, restart treatment at 20 mg QD (1 tablet)
Third appearance	Consider permanent discontinuation
* If cobimetinib is withheld for > 28 days because of toxicity, the patient should be discontinued from cobimetinib, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator.	

5.5.2 Dose Modifications for Atezolizumab

There will be no dose modifications for atezolizumab.

Table 3: Recommended guidelines for management of general adverse events Atezolizumab Dose Modifications.

Grade (CTCAE)	Recommended dose modification
Grade 1 or 2	No action required

Grade 3 and 4	• Interrupt dosing of atezolizumab. • If AE resolves to Grade ≤ 1, then restart dosing of atezolizumab at fixed dose level. • If the AE does not resolve to Grade ≤ 1 permanently discontinue atezolizumab. • If the Grade 3/4 AE recurs (a second time), atezolizumab should be discontinued.

Additional guidelines for specific adverse events are provided in the subsections below and the specific management guidelines are highlighted in Appendix 7 for cobimetinib plus atezolizumab.

5.5.3 Specific Dose Modifications for 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, may be used to determine a possible immunogenic etiology. Although most immune−mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have immediate therapeutic effect, and in severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The primary approach to Grade 1 and 2 immune−mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune−mediated adverse events, atezolizumab should be withheld and oral/parenteral steroids administered. Recurrent Grade 2 immune−mediated adverse events may also mandate withholding atezolizumab or the use of steroids. Consideration for benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab.

Atezolizumab should be permanently discontinued in patients with life-threatening immune−mediated adverse events. Patients who discontinue atezolizumab treatment may still remain in the study until loss of clinical benefit. Management of systemic immune activation is presented below.

See the atezolizumab Investigator's Brochure and Appendix 7 for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events. See Appendix 8 for precautions for anaphylaxis.

Systemic Immune Activation

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

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

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

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

5.5.4 Specific Dose Modifications for cobimetinib

Withhold cobimetinib for NCI CTCAE intolerable Grade ≥ 2 toxicity.

When restarting therapy after withholding treatment for a toxicity that has resolved to baseline or grade ≤ 1:

- Reduce cobimetinib dose to 40 mg
- Reduce cobimetinib to 20 mg for second appearance of intolerable Grade ≥ 2 toxicity.
- Permanently discontinue cobimetinib on third appearance of intolerable Grade ≥ 2 toxicity unless the benefits for the individual patient are deemed to outweigh the risks.

For detailed recommendations regarding management of certain AEs, i.e. gastrointestinal toxicity (diarrhea), hepatotoxicity, rash, pulmonary toxicity, eye toxicity and cardiotoxicity, see Appendix 7.

5.6 STUDY ASSESSMENTS

Signed, IRB-approved informed consent must be obtained from patients prior to the pretreatment assessments. The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

5.6.1 Informed Consent Forms and Screening Log

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

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

Re-screening is required if a patient has not met all of the eligibility criteria within 28 days from the original date of the screening visit. Re-screening refers to repeating the entire screening process with the exception of performing a repeat biopsy to collect a tumor tissue sample to be used to determine PD-L1 status and repeating CT and/or MRI imaging scans used for tumor assessment, provided the biopsy tissue sample and imaging scans were obtained during the original screening visit. Patients are only allowed to be re-screened twice. Blood samples may be redrawn due to sample handling problems, breakage, or sample integrity, without being considered a re-screen.

5.6.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

5.6.3 Physical Examinations

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

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

5.6.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Height will be assessed at baseline, and weight will be assessed at each study visit.

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

5.6.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and every 8 weeks in all cohorts assessed, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for atezolizumab treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

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.

Cross sectional imaging will be performed with either contrast enhanced CT or MRI. RECIST 1.1 criteria will be used to determine disease response.

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

All measurable and evaluable lesions should be re assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Response will be assessed by a blinded radiologist at the MD Anderson Quantitative Imaging Analysis Core using RECIST v1.1 (see Appendix 2) and immune-modified RECIST (see Appendix 5). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

For cutaneous squamous cell carcinoma, since "surgery (preferable) or definitive radiation therapy (with or without radiosensitizing agent)" is allowed for patients after initial response, such a definitive local therapy can only be performed after at least 1 tumor assessment.

5.6.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, 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, CPK
- Coagulation: INR, aPTT, fibrinogen, D-dimer
- 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, total HBcAb. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- 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.
- Pregnancy test. All women of childbearing potential will have a serum/urine pregnancy test at screening. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
- *The following samples will be sent to one or several central laboratories or to the Genentech Inc. for analysis:*
- ***Blood*** samples for translational research on biomarkers (See Appendix 9).
- Tumor tissue samples will be collected for exploratory research on biomarkers (See Appendix 9).

a. Fresh tumor tissue sample (or archival tissue) will be collected at baseline for determination of PD L1 expression and for exploratory research on biomarkers

- Tissue should be collected by excisional or core needle biopsy, typically using a 21-18 gauge needle. The biopsy should include at least 5 cores, 2 FFPE and 3 fresh frozen. It should be collected within 28 days prior to initiation of protocol therapy.
- For archival tissue: a representative FFPE tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections need to be submitted along with an associated pathology report. Tumor tissue should be of good quality based on total and viable tumor content. Samples should ideally contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable.
- Considering the benefit seen with immunotherapy in MSI-H colon cancer, we will perform MSI tests on patients with small bowel and appendiceal adenocarcinoma.

b. Tumor tissue sample will also be collected at week 4 for exploratory research on biomarkers

- Biopsies at week 4 should be performed within 7 days before administration of C2D1 of study therapy. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

c. Tumor tissue sample will also be collected at time of progression for exploratory research on biomarkers

- Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.
- For cutaneous squamous cell carcinoma, where local therapy options may be considered in the future, the lesions biopsied will be documented at each time point and if possible, a sample will be collected in patients who go to surgery. The location of the sample collected at surgery will also be documented.

Blood and tissue collections will be tracked by Tissue Station. Collection requests will be placed in the system, prior collections, and updated once completed including details of the process. All samples shipped to Genentech will be tracked and documented in Tissue Station,

Exploratory biomarker research may include, but will not be limited to, immunohistochemistry for PD-L1, multiplexed immunofluorescence for immune markers, flow cytometry, analysis of ctDNA concentration, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of germline or somatic mutations, and use of WGS or NGS.

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

Biological samples will be destroyed when the final manuscript has been completed, with the following exceptions:

- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- ***Blood, plasma, serum, and tumor tissue*** samples collected for biomarker research will be destroyed no later than 5 years after the final manuscript has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards.

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.

5.6.7 Assessments during Screening and Treatment

The following are recommended evaluations (Please refer to the current atezolizumab and cobimetinib Investigator's Brochures for guidance to the investigator on the management of safety concerns associated with atezolizumab and cobimetinib therapy):

- Physical examination: Routine physical is needed.
- Monitor complete blood count (CBC), chemistries, and liver function test, etc. per institutional guidelines
- Ophthalmologic examination – Screening, C2D1, then q 3 cycles and as clinically indicated
    - ***a.*** Ophthalmologic examinations will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (OCT). If spectral domain OCT is not available, time-domain OCT may be performed instead. Ophthalmologic examination must be performed by a qualified ophthalmologist.
- LVEF – Evaluate left ventricular function using echocardiogram (ECHO) or MUGA. All patients will undergo evaluation of left ventricular dysfunction by ECHO at screening. Further, evaluation of LVEF by ECHO must be performed at the following timepoints: Cycle 2, Day 1 ± 1 week; Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ± 2 weeks; Day 1 of Cycles 15+ (every 4 treatment cycles) ± 2 weeks.
- Unscheduled Assessments

- A clinic visit should be scheduled any time there is a safety issue or any unscheduled assessments need to be performed as well as tumor assessments as clinically indicated.

5.6.8 Follow-Up Assessments

Please see Appendix 1 for the schedule of assessments performed during the study.

- **For progression-free survival follow-up**

  Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by PI, or death, whichever occurs first.

- **For survival follow-up**

  Patients who discontinue study treatment for reasons other than withdrawal of consent will be followed for survival and subsequent ant-cancer therapies approximately every 3 months until death, loss to follow–up, withdrawal of consent, or study termination by PI. During this period, documentation of anti-cancer therapies should include administration start and stop dates.

  Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first.

5.7 DISCONTINUATION OF PROTOCOL-SPECIFIED THERAPY

Protocol-specified therapy may be discontinued for any of the following reasons:

- Progressive disease (See section 5.3.4 for treatment beyond RECIST progression).
- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)
- Physician's judgment

5.8 PATIENT DISCONTINUATION

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study
- Investigator determines it is in the best interest of the patient
- Patient non-compliance

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

5.9 STUDY DISCONTINUATION

Genentech, Study Center, and the Principal Investigator and the MD Anderson IND Office (as the IND Sponsor) have the right to terminate this study at any time. Reasons for terminating the study may include the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording are inaccurate or incomplete
- Study protocol not followed

5.10 STATISTICAL METHODS

5.10.1 Analysis of the Conduct of the Study

This is a single-arm, Phase IIA, single-center, open-label study designed to evaluate the safety and efficacy of cobimetinib plus atezolizumab in approximately 20 patients per cohort of advanced rare cancers.

The efficacy analyses of OS, PFS, and ORR will be performed on all treated patients. DOR will be assessed in patients who have an objective response. The safety population will include all patients who received any amount of study drug. Patients who are enrolled into the study but do not receive any amount of study drug will not be included in the safety population.

5.10.2 Efficacy Analysis

5.10.2.1 Primary Endpoint

- ORR (PR or CR) per RECIST v1.1.

5.10.2.2 Secondary Endpoints

- Efficacy Endpoints:
  - **a.** ORR per irRECIST.
  - **b.** PFS per RECIST v1.1 and irRECIST.
  - **c.** OS
  - **d.** DCR and DOR per RECIST v1.1 and irRECIST.
- Safety Endpoints:
  - **a.** Adverse events per CTCAE v4.0.
- Translational Endpoints:
  - **a.** Tumor tissue and peripheral blood

5.10.3 Determination of Sample Size

The primary endpoint is best ORR (PR or CR), measured as per RECIST 1.1. Three parallel single-stage phase II trials will be conducted. A total of 60 patients will be enrolled, i.e., 20 patients in each tumor group. Considering the rareness of the disease, the patient accrual rate is approximately 1 to 2 patients per month per tumor group.

Sample size calculation

For each tumor group, we will estimate the best ORR and its exact confidence interval (CI). When the sample size is 20, and the response rate is 0.3, the two-sided 95% exact CI using the Clopper and Pearson method will be (0.119, 0.543).

For each tumor group, we will also compare its overall best response rate to the historical control based on the current literature. Let p represent the overall best response rate, we will perform independent Binomial test against H0: p=0.1 for each group, with a 1-sided type I error rate of 0.05. The sample size of 20 will provide 76% power to detect an improved best ORR being 30% compared to 10%.

Analysis Plan

The primary outcome is the best ORR since the start of treatment. For each tumor group, we will estimate the best response rate and its 95% exact confidence interval using the Clopper and Pearson method. And we will assess the efficacy of the combination treatment by performing the independent binomial test comparing the best response rate versus the historical control for each tumor group. The primary efficacy analyses will include all treated patients who have received at least one dose of study treatment and have baseline tumor assessment. Patients who do not receive at least 1 dose of therapy will be replaced.

For each tumor group, median DOR and corresponding 2-sided 95% CI will be reported. The association between the best ORR and other variables will be assessed using the Fisher's exact test. Time-to-event outcomes, including progression free survival (PFS) and overall survival (OS), will be estimated using Kaplan-Meier method. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model may be utilized to include multiple covariates in the time-to-event analysis.

Patients' demographic information (e.g. age, gender) at baseline will be analyzed, with data summarized in mean ± standard deviation, median and range for continuous variables, and in frequency count and percentage for categorical variables. The student t-test or the Wilcoxon test may be used to compare continuous variables among different tumor patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

The safety analyses will include all treated patients who received at least one dose of study treatment. Toxicity data will be summarized by frequency tables for each tumor type group. The association between the types and severity of toxicity and the tumor group will be evaluated. No formal statistical testing will be performed on these summaries.

Summary statistics for biomarkers and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each tumor group. The time-course of biomarker measures will be investigated graphically. If there is indication of meaningful pattern over time, further analysis (eg, by linear mixed model) may be performed to characterize the relationship. Methods such as, but not limited to, logistic regression will be used to explore possible associations between biomarker measures and clinical outcomes.

MDACC Investigational New Drug (IND) office will review safety/efficacy data with Principal Investigator (and statistician if needed) at a predetermined interval as indicated next. The first analysis will occur after the first 5 subjects are treated for at least 2 cycles, per tumor group. Reports submission will continue in cohort size of 5, per tumor group, thereafter. On every report submission, the information from previous reported patients will need to be updated.

Considering the limited sample size for each tumor group, we may apply the Bayesian classification and information sharing method proposed by Lee and Chen (submitted) in the data analysis. It will provide a more efficient and more powerful way to estimate and test the response

rate for similarly performed groups. We will first cluster the tumor groups according to their response rate into the low- or high-response cluster first, and then apply the Bayesian hierarchical model to borrow information among groups within the same cluster in estimating their response rate and comparing it to the historical control.

5.10.4 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the PI may choose to conduct up to two interim efficacy analyses. The interim analysis will be performed and interpreted by members of the study team.

5.10.5 Interim Safety Monitoring

For patient safety, A Bayesian toxicity monitoring rule will be implemented for the treatment related toxicity events during the duration of the treatment in all treated patients across 3 tumor groups.

The toxicity event is defined as AESIs for the combination of atezolizumab and cobimetinib may include the following:

- Non-hematologic AEs Grade ≥ 3 with the exceptions of:
- Grade 3 Nausea
- Grade ≥ 3 Diarrhea if reversible within 48 hours with maximal supportive care
- Electrolyte abnormalities that are reversible within 72 hours with supportive care and/or supplementation
- All hematologic AEs Grade ≥ 4
- Specific toxicities:
    - Grade 1−4 serous retinopathy
    - Any grade retinal vein occlusion (RVO)
    - Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis and left ventricular dysfunction)
    - Rhabdomyolysis or elevated CPK
    - Grade ≥ 3 hemorrhagic event or any grade cerebral hemorrhage
    - Systemic lupus erythematosus
    - Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
    - Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, or infusion-reaction syndromes
    - Ocular toxicities (e.g. uveitis, retinitis)
    - Myositis
    - Grade ≥ 3 Hepatotoxicity
    - Grade ≥ 3 rash
    - Pneumonitis

- Colitis
- Nephritis
- Endocrinopathies (diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism or hypophysitis)

Let p.tox be the toxicity probability, then if Pr [p. tox > 0.3] >0.9, we will terminate the study early. We will apply the monitoring every 5 patients. That is, we will early stop the study if we observe [# patients experiencing toxicity] / [#patients being treated] >= 4/5, 6/10, 8/15, 9/20, 11/25, 13/30, 115/35, 16/40, 18/45, 20/50, 22/55, or 23/60. The operating characteristic for applying this toxicity monitoring rule is shown in Table 2.

Table 2. Operating characteristics for toxicity early stopping based 5000 simulation runs per scenario

True toxicity probability	Early stopping probability	Average sample size
0.2	0.024	58.9
0.3	0.238	51.1
0.4	0.730	32.4
0.5	0.973	18.1

6. ASSESSMENT OF SAFETY

6.1.1 Risks Associated with Atezolizumab

Refer to the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

6.1.2 Risks Associated with Cobimetinib

The following adverse events are classified as identified risks associated with cobimetinib: serous retinopathy, left ventricular dysfunction, photosensitivity (when administered with vemurafenib), severe hemorrhage, rhabdomyolysis, and pneumonitis. The following adverse events are classified as potential risks for cobimetinib: severe hepatotoxicity (Grade $\geq$3), impaired female fertility, and teratogenicity and developmental toxicity. In addition, there is the possibility of drug-drug interactions in patients treated with cobimetinib. Refer to Section 6 of the cobimetinib Investigator's Brochure for a detailed description of all anticipated risks for cobimetinib.

6.1.2.1 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.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to evaluate for risk factors for neurosensory retinal

detachment. Patients will also undergo complete ophthalmologic examinations at specified timepoints throughout the study and as clinically indicated if a patient notes any visual disturbances. Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 5.6.7 and the Appendix 1, Study Flowchart.

Guidelines for management of patients who develop serous retinopathy are provided in Appendix 7.

6.1.2.2 Left Ventricular Dysfunction

Decrease from baseline in left ventricular ejection fraction has been reported in patients receiving cobimetinib. Decreased left ventricular ejection fraction may be symptomatic or asymptomatic.

All patients will undergo evaluation of left ventricular ejection fraction, either by echocardiography or multigated acquisition scan at baseline, at specified timepoints during treatment, at the end of treatment, and as clinically indicated.

Guidelines for management of patients who have decreases in left ventricular ejection fraction are provided in Appendix 7.

6.1.2.3 Photosensitivity (When Administered with Vemurafenib)

No evidence of photosensitivity has been observed with cobimetinib as a single agent. However, photosensitivity has been observed when cobimetinib was given in combination with vemurafenib.

6.1.2.4 Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were reported as non-serious and a lower severity (grade).

Guidelines for management of patients who develop pulmonary events (including pneumonitis) are provided in Appendix 7.

6.1.2.5 Rhabdomyolysis

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141, and rhabdomyolysis has been reported in postmarketing experience. CPK will be monitored at baseline and monthly during treatment or as clinically indicated.

Guidelines for management of patients who develop CPK elevations or rhabdomyolysis are provided in Appendix 7.

6.1.2.6 Hemorrhage

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

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

Instructions for dose modification for hemorrhage events are included in Appendix 7.

6.1.2.7 Severe Hepatotoxicity (Grade ≥3)

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 and vemurafenib. Generally, elevations in liver laboratory tests have been managed effectively with dose modifications.

Guidelines for management of patients who develop elevations in ALT, AST, and/or bilirubin are provided in Appendix 6.

6.1.2.8 Impaired Female Fertility

Results from nonclinical studies indicate that there is a potential for effects on female fertility. While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes were observed in reproductive tissues of dogs. These changes were reversible upon discontinuation of cobimetinib.

6.1.2.9 Teratogenicity and Developmental Toxicity

There are no data regarding the use of cobimetinib in pregnant women. When cobimetinib was administered to pregnant rats, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at similar systemic exposures 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.

6.2 SAFETY PARAMETERS AND DEFINITIONS

6.2.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to atezolizumab and/or cobimetinib, all events of death, AEs of Special Interest (AESIs), and any study specific issue of concern.

6.2.2 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with rare cancers that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to the first dose of atezolizumab and/or cobimetinib associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

6.2.3 Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death (i.e., the AE actually causes or leads to death)
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

6.3 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed and reported during the study are collected, recorded on the Adverse Event eCRF, and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Investigators will seek information on adverse events at each patient contact. All adverse events (all grades and attributions), 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.

6.3.1 Adverse Event Reporting Period

All AEs and SAEs where the patient has been exposed to Genentech product must be reported Reporting period begins after informed consent is obtained and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment

During screening AEs are not recorded unless they are SAEs which are related to protocol-mandated procedures. ALL AEs (including SAEs) must be recorded from the time of first atezolizumab and cobimetinib administration and end 30 days following the last administration of atezolizumab and/or cobimetinib or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

6.3.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the atezolizumab and/or cobimetinib (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes (Definitive /Probable/Possible and Unlikely)

There is a plausible temporal relationship between the onset of the AE and administration of the atezolizumab and/or cobimetinib, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the atezolizumab and/or cobimetinib or with similar treatments; and/or the AE abates or resolves upon discontinuation of the atezolizumab and/or cobimetinib or dose reduction and, if applicable, reappears upon re-challenge.

No (Unrelated)

Evidence exists that the AE has an etiology other than the atezolizumab and/or cobimetinib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab and/or cobimetinib administration (e.g., cancer diagnosed 2 days after first dose of study treatments).

Expected AEs are those AEs that are listed or characterized in the Package Insert or current Investigator's Brochure.

Unexpected AEs are those not listed in the Package Insert or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the Package Insert or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the Package Insert or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy, i.e. atezolizumab and cobimetinib.

6.4 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

6.4.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

6.4.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Please record adverse events as per recommended Adverse Event Recording Guidelines seen in table below.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I Phase II	Phase I Phase II	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I Phase II	Phase I Phase II	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

6.4.2.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported 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, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

6.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 6.3.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

6.4.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

6.4.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

6.4.2.5 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. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

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

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

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

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

6.4.2.6 Pregnancy

If a female patient or a female partner of the male patient becomes pregnant while receiving investigational therapy or within 6 months after the last dose of atezolizumab or within 2 weeks after the last dose of cobimetinib, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to the atezolizumab and/or cobimetinib should be reported as an SAE.

6.4.2.7 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior atezolizumab and/or cobimetinib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient (including pregnancy occurring in female partner of a male patient) who participated in the study, this should be reported as an SAE adequately to Genentech Drug Safety during follow up period.

6.4.2.8 Reporting to Genentech

A safety data exchange agreement (SDEA) is in place for this study. Guidance on reporting requirements to Genentech is referenced in the SDEA.

6.4.2.9 Reconciliation Case Transmission Verification The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the

reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

6.4.2.10 Adverse Events of Special Interest (AESIs)

AESIs are defined as a potential safety problem, identified as a result of safety monitoring of atezolizumab and cobimetinib.

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted. AESIs are to be reported within the same reporting timeframe as SAEs (See Section 6.4.3)

AESIs for the combination of atezolizumab and cobimetinib may include the following:

- Non-specific AEs of Special Interest
    - Events suggestive of potential drug-induced liver injury (DILI) or other Grade ⩾ 3 hepatotoxicity that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
        - Treatment-emergent ALT or AST ⩾ 3 X baseline value in combination with total bilirubin ⩾ 2 X ULN (of which ⩾ 35% is direct bilirubin)
        - Treatment-emergent ALT or AST ⩾ 3 X baseline value in combination with clinical jaundice
    - Suspected transmission of an infectious agent by the study treatment, defined as: 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
- AESIs specific to Cobimetinib:
    - Any grade Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathyAny grade retinal vein occlusion (RVO)
    - • Symptomatic heart failure / Grade ⩾ 2 left ventricular dysfunction
    - Rhabdomyolysis or elevated CPK
    - Includes Grade ≥ 3 elevations of 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
- Grade ⩾ 3 Diarrhea
- Pneumonitis
- Grade ⩾ 3 photosensitivity (when administered with vemurafenib)
- Significant liver toxicity: AST and/or ALT > 10 X upper limit of normal

- AESIs specific to Atezolizumab:
  - Pneumonitis
  - Colitis
  - Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism and hypophysitis
  - Hepatitis, including AST or ALT > 10 × ULN
  - Systemic lupus erythematosus
  - Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
  - Events suggestive of hypersensitivity, infusion related reactions, cytokine release, influenza-like illness and systemic inflammatory response syndrome.
  - Nephritis
  - Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
  - Myositis
  - Myopathies, including rhabdomyolysis
  - Grade ≥2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
  - Vasculitis
  - Autoimmune hemolytic anemia
  - Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

6.4.3 Exchange of single case reports

Investigators must report all SAEs and AESIs using internal eSAE reporting forms and these will be forwarded electronically to the IND office and to Genentech within the timelines described below.

MDACC will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to: **E-mail:** usds_aereporting-d@gene.com

OR

Fax: (650) 238-6067

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

All SAEs, AESIs and pregnancy reports (including pregnancy occurring in the partner of a male study subject) where the patient has been exposed to the Genentech Product, shall be transmitted to Genentech on a MedWatch or CIOMS I or on Genentech approved SAE form within one (1) business day of the awareness date.

Additional Reporting Requirements to Genentech include the following:

- **Non-serious AEs**:
  All Non-serious AEs originating from the Study will be forwarded in a quarterly report to Genentech.

  Note: Investigators should also report events to their IRB as required.

- **Special Situation Reports**:
  In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the Product usage during breastfeeding
  - Data related to overdose, off-label use, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
  - Lack of therapeutic efficacy. In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

- **Product Complaints:**
  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within one (1) business day of the awareness date.

6.4.4. IND ANNUAL REPORTS

Copies to Genentech:

All IND annual reports submitted to the FDA should be copied to Genentech. Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mailbox:

ctvist_drugsafety@gene.com

MDACC will forward a copy of the Final Study Report to Genentech upon completion of the Study.

6.5 STUDY CLOSE-OUT

Any study report submitted to the FDA should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Email: anti-pdl-1-mpd3280a-gsur@gene.com

Fax: 610-639-3194

And to Genentech Drug Safety CTV oversight mail box at :
ctvist_drugsafety@gene.com

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The University of Texas MD Anderson Cancer Center will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. The PI will perform oversight of the data management of this study.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at The University of Texas MD Anderson Cancer Center and records retention for the study data will be consistent with The University of Texas MD Anderson Cancer Center's standard procedures, which mandate that data be maintained indefinitely.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of the MD Anderson Cancer Center Prometheus EDC system.

Designated, trained site staff should complete all eCRFs. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

SAE data will be captured via eSAE in accordance with Sponsor policy.

7.3 SOURCE DATA DOCUMENTATION

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator indefinitely, in accordance with the current policy of the MD Anderson Cancer Center IND office.

Written notification should be provided to the Sponsor and Genentech Inc prior to transferring any records to another party or moving them to another location.

7.6 MONITORING

During the study, a study monitor from the University of Texas MD Anderson Cancer Center Investigational New Drug Office will have regular contacts with the investigator and team.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority

requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

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

8.4 CONFIDENTIALITY

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

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

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

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 Roche policy on study data publication (see Section 9.4).

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor and Genentech Inc. 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., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and Genentech Inc. and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 ADMINISTRATIVE STRUCTURE

This trial will be supported via the rare disease strategic alliance between The University of Texas MD Anderson Cancer Center and Genentech. The University of Texas MD Anderson Cancer Center will be the sole site, responsible for enrolling approximately 60 total patients.

The MD Anderson Cancer Center IND office will provide oversight of safety (see Section 6.0).

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After written informed consent has been obtained, the study team will generate a unique study identification number for the patient.

Patient data will be recorded via an EDC system with use of eCRFs.

Central laboratories, including those at Genentech/Roche/Roche collaborators and at The University of Texas MD Anderson Cancer Center, will be used for PD-L1 expression status determination and will provide kits for pharmacogenomics, tissue, whole blood, serum, and plasma sample analyses to be conducted at central laboratories or Genentech Inc.

Treatment decisions will be made on the basis of the local reading of ECGs obtained during the study.

Imaging data will be retained at The University of Texas MD Anderson Cancer Center.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

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

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the principal investigator 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 principal investigator 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 Genentech Inc. prior to submission for publication or presentation. This allows Genentech Inc. 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, Genentech Inc. 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 Genentech Inc. personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Genentech Inc. 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 Genentech Inc., except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

The principal investigator will prepare any protocol amendments. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

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

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Appendix 1 Study Flowchart

Day	Screening	Treatment Period						Study Completion or Early Term Visit (within 2 wks. after last dose of study drug)	Follow-Up[k]
	Day -28 to -1	C1D1 ±3day	C1D15 ±3d	C2D1 ±3d	C2D15 ±3d	C3+D1[l] ±3d	C3+D15 ±3d		
Informed consent	X								
Demographic data	X								
Medical history	X								
Vital signs[a]	X	X	X	X	X	X	X	X	
Weight & height[a]	X	X	X	X	X	X	X	X	
Physical examination[b]	X			X		X		X	
ECOG performance status	X			X		X			
Hematology[c]	X		X	X	X	X[p]	X	X	
Chemistry[d]	X		X	X	X	X[p]	X	X	
Coagulation[e]	X			X		X[p]		X	
TSH, Free T4, Free T3	X	Every 4 cycles						X	
Viral Serology	X								
Urinalysis	X			X		X[p]		X	
Pregnancy Test[o]	X								
ECHO[f]	X	See Note						X	
Cobimetinib[g]		See Note							
Atezolizumab[g]		X	X	X	X	X	X		
Response assessment[h]	X	Scans will be done every 8 weeks[p]						X	
Complete Opthalmologic Eval[i]	X			X		Every 3 cycles			
Concomitant medications[j]	X			X		X		X	
Adverse events	X			X		X		X	X

Day	Screening	Treatment Period						Study Completion or Early Term Visit (within 2 wks. after last dose of study drug)	Follow-Up[k]
	Day -28 to -1	**C1D1 ±3day**	**C1D15 ±3d**	**C2D1 ±3d**	**C2D15 ±3d**	**C3+D1[l] ±3d**	**C3+D15 ±3d**		
Blood Sample (Translational)		X	X					X (at progression)	
Baseline tumor tissue sample[m]	X								
Tumor biopsy (if feasible)[n]				X				X	

Day	Screening	Treatment Period						Study Completion or Early Term Visit (within 2 wks. after last dose of study drug)	Follow-Up[k]
	Day -28 to -1	C1D1 ±3day	C1D15 ±3d	C2D1 ±3d	C2D15 ±3d	C3+D1[l] ±3d	C3+D15 ±3d		

Define each assessment in footnotes

[a] Heart rate, systolic/diastolic blood pressure while patient in seated position, and temperature. Height to be taken at baseline (no repeat measures needed).

[b] Physical examination only on day 1 of each cycle. If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

[c] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count.

[d] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.

[e] Prothrombin time/International Normalized Ratio, Partial thromboplastin time, fibrinogen, D-dimer.

[f] All patients will undergo evaluation of left ventricular dysfunction by ECHO at screening. Further, evaluation of LVEF by ECHO must be performed at the following timepoints: Cycle 2, Day 1 ± 1 week; Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ± 2 weeks; Day 1 of Cycles 15+ (every 4 treatment cycles) ± 2 weeks. If cobimetinib is permanently discontinued due to toxicity, starting 3 weeks after last dose, perform ECHO only if clinically indicated.

[g] Cobimetinib is taken by mouth daily for 21 days and then 1 week off. For patient who have discontinued cobimetinib, atezolizumab can be given IV at 1680 mg once every 4 weeks.

[h] Response assessment by cross-sectional imaging such as CT, MRI, or PET-CT as per standard of care for each disease. Imaging may occur up to 72 hours prior to scheduled day. Baseline assessment must occur within 28 days prior to day 1.

[i] Complete ophthalmologic exams will be performed at baseline (screening), C2D1 (+/- 1 week), then q 3 cycles (+/- 2 weeks). Ophthalmologic examinations will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (OCT). If spectral domain OCT is not available, time-domain OCT may be performed instead. Ophthalmologic examination must be performed by a qualified ophthalmologist. If cobimetinib is permanently discontinued due to toxicity, starting 3 weeks after last dose, perform ophthalmologic exam only if clinically indicated.

[j] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening

[k] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first.

[l] Labs and restaging need not be repeated every 3rd cycle if they have been performed within 3 days as a part of restaging.

[m] A pretreatment tumor biopsy is required. If pretreatment biopsy cannot be performed and archival tissue is available, archival tissue will be collected. Refer to Section 5.6.6 for tissue sample requirements.

[n] Screening biopsy is needed only if archival tumor tissue is unavailable or is determined to be unsuitable for required testing. On-treatment biopsy will be obtained during week 4 (within 7 days prior to Cycle 2 Day 1). Patients will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of confirmed radiographic disease progression. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 5.6.6 for tissue sample requirements.

[o] Pregnancy test can be a urine/serum pregnancy test.

[p] Assessments can be performed upto 7 business days prior to C3D1. Blood for translational studies can be collected within +/-1 week.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST Criteria)

The RECIST criteria should be used to assess response to treatment. Only patients with measurable disease should be entered in the study. Measurable disease is defined as the presence of one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques (or as ≥1.0 cm by spiral CT). Evaluable lesions should be followed for the assessment of response. Non-measurable lesions include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitic carcinomatosis, abdominal masses that are not confirmed by CT, and cystic lesions.

All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

- Complete response (CR)

  Disappearance of all evidence of tumor for at least two cycles of therapy. Tumor markers must be normal.

- Partial response

  At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

- Stable disease (SD)

  Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

- Progressive disease (PD)

  At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the beginning of treatment or the appearance of one or more new lesions.

- Clinical progressive disease

  Patients, who in the opinion of the treating physician investigator have had a substantial decline in their performance status and have clinical evidence of progressive disease may be classified as having progressive disease.

Appendix 3 National Cancer Institute Common Toxicity Criteria for Adverse Events

Version 4 of the NCI-CTC-AE can be obtained from:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix 4 Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥30% decrease in tumor burden, [a] in the absence of CR
PD	≥20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$5 mm)

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

20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 mm but $<$15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered

measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

Chest CT is preferred over 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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is

based on the assumption that CT slice thickness is ≤5 mm. When CT scans have slice thickness of >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (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 if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are

defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 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.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non–lymph node lesions must be ≥10 mm on the longest diameter; new lymph nodes must be ≥15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥10 mm and <15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is <10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥15 mm.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is ≥15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to <15 mm (or even <10 mm). However, if it subsequently decreases to <10 mm and all other lesions are no longer detectable or have also decreased to a short axis of <10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to <10 mm during the study. Thus, when lymph nodes are included in the sum of diameters, the sum may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non–lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

Definitions of the criteria used to determine objective tumor response are provided below:

Complete response (CR): Disappearance of all lesions

Any pathological lymph nodes must have reduction in short axis to <10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR

Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)

In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

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

Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

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

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 1.

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Appendix 5 Safety Reporting Fax Coversheet

Genentech
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Genentech Supported Research
AE/ SAE FAX No: (650) 238-6067

Email: usds_aereporting-d@gene.com

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter Name	
Reporter Telephone #	
Reporter Fax #	
• Initial Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]
• Follow-up Report Date	[INSERT investigational product name] / [INSERT investigational product name] / [INSERT investigational product name]
Patient Initials (Please enter a dash if the patient has no middle name)	[INSERT investigational product name] - [INSERT investigational product name] - [INSERT investigational product name]

SAE or Safety Reporting questions, contact Genentech Safety: **(888) 835-2555**

PLEASE PLACE eSAE REPORT BEHIND THIS COVER SHEET

Version 2 05-May-2015

Appendix 6 Management of Cobimetinib plus Atezolizumab−Associated Adverse Events

Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
General guidance for dose modifications and treatment delays and discontinuation	• There will be no dose modifications for atezolizumab. • If atezolizumab is withheld and corticosteroids are initiated for an atezolizumab-related toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. [a, b, c] • The dose of cobimetinib can be reduced by 20 mg (one dose level) up to two times (i.e., from 60 mg to 40 mg and then from 40 mg to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab at the investigator's discretion. • If cobimetinib is withheld for > 28 days because of toxicity, the patient should be discontinued from cobimetinib, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator.
IRRs, anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs are provided in the Atezolizumab Investigator's Brochure for atezolizumab. • For anaphylaxis precautions, see Appendix 8. • For severe hypersensitivity reactions, permanently discontinue all study treatment.

IRR = infusion-related reaction.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL TOXICITY

Diarrhea and colitis have been associated with the administration of cobimetinib plus atezolizumab.

Diarrhea can frequently be managed with anti-diarrheal agents but can also progress to clinically significant dehydration and/or electrolyte imbalances with effects on other organs, possibly resulting in renal, hepatic, and/or cardiac failure. Patients should be instructed to promptly contact the investigators if they develop diarrhea. Investigators should treat diarrhea and intervene promptly for patients who appear to be at increased risk of developing significant dehydration, electrolyte imbalances, and/or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

See Table A3-1 for guidelines on how to manage gastrointestinal toxicity in patients treated with cobimetinib plus atezolizumab.

Table A3-1 Guidelines for Managing Atezolizumab- and Cobimetinib-Associated Gastrointestinal Toxicity

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist □ 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Colitis, Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEPATOTOXICITY

Hepatoxicity has been associated with the administration of atezolizumab and cobimetinib. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment.

While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for the increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should considered.

Patients with LFT abnormalities should be managed according to the guidelines in
Table A3-2.

Table A3-2 Guidelines for Managing Atezolizumab and Cobimetinib–Associated Hepatotoxicity

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	

AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN (Grade 1)	• Continue atezolizumab and cobimetinib. • Continue with the standard monitoring plan (i.e., LFTs q4w before dosing).
AST/ALT > 3 × baseline values to < 5 × ULN with total bilirubin < 2 × ULN (Grade 2)	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune related events of > 5 days duration o Consider withholding atezolizumab [c] o Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper o Restart atezolizumab if event resolves to Grade 1 or better within 12 weeks [a, b] o Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]
AST/ALT > 5 × baseline values to < 10 × ULN with total bilirubin < 2 × ULN (Grade 3)	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune related events o Withhold atezolizumab o Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper o 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. o Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]
AST/ALT > 3 × ULN with bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Consult hepatologist and consider liver biopsy. • Consider administering 1-2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper (for possible autoimmune hepatitis). • If LFTs do not decrease within 48 hr after initiation of systemic steroids, consider adding an immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist). • Monitor LFTs every 48–72 hr until decreasing and then follow weekly. • Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction after discussion with medical monitor if AST/ALT < 3 × ULN with bilirubin < 2 × ULN and steroid dose < 10 mg oral prednisone equivalent per day. [a, b, c] • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events, and contact the Medical Monitor.

AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib. [c] • Consult hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent (for possible autoimmune hepatitis). If event resolves to Grade 1 or better, taper corticosteroids over ≥ _1 month. • If LFTs do not decrease within 48 hr after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) or dose escalation of corticosteroids may be considered. • Monitor LFTs every 48–72 hr until decreasing and then follow weekly.

ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC TOXICITY

Treatment-emergent rash has been associated with atezolizumab and cobimetinib. The majority of the cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Dermatologic toxicity and rash should be managed according to the guidelines in
Table A3-3.

Table A3-3 Guidelines for Managing Atezolizumab and Cobimetinib Rash

Event	Action to Be Taken
Dermatologic toxicity	
Dermatologic event, Grade 1/2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For grade 2 rash, consider referral to dermatologist. **Acneiform rash:** • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a,b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c] • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. **Acneiform rash:** • Consider continuation of topical corticosteroids (e.g., hydrocortisone 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c]

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PULMONARY TOXICITY

Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution computed tomography (CT) scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy (if clinically feasible)
- Pulmonary function tests (diffusion capacity of the lung for carbon monoxide)
- Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Pulmonary toxicity should be managed according to the guidelines in Table A3-4.

Table A3-4 Guidelines for Managing Atezolizumab− and Cobimetinib−Associated Pulmonary Toxicity

Pulmonary events	
Pneumonitis, grade 1	• Continue atezolizumab and cobimetinib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as Grade 3 or 4 event.

Pneumonitis, grade 2	• Withhold atezolizumab and cobimetinib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and cobimetinib if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • For recurrent events, treat as a Grade 3 or 4 event.
Pneumonitis, grade 3/4	• Permanently discontinue atezolizumab and cobimetinib.[c] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If pulmonary event does not improve within 48 hr or worsens, consider adding an immunosuppressive agent (e.g., infliximab, cyclophosphamide, IV Ig, or mycophenolate mofetil). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

POTENTIAL EYE TOXICITY

An ophthalmologist should evaluate visual complaints.

Uveitis or episcleritis and other immune−mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Serous retinopathy have been associated with cobimetinib.

Potential ocular toxicity should be managed according to the guidelines in Table A3-5.

Event	Action to Be Taken
Ocular toxicity	
Serous retinopathy Severity grade assessment based on NCI CTCAE v4 "Eye Disorders – Other" scale [d, e, f, g]	**Serous retinopathy, Grade 1 [d] or 2 [e] (tolerable):** • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated. **Serous retinopathy, Grade 2 [e] (intolerable) or 3/4 [f/g]:** • Interrupt cobimetinib until grade ≤1. • Continue atezolizumab as clinically indicated. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Cobimetinib should be dose reduced by 1 dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite 2 dose level reductions
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Continue cobimetinib as clinically indicated.
Retinal vein occlusion (any grade)	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab.

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; OCT = optical coherence tomography.

[d] Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

[e] Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.

[f] Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL.

[g] Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE DECREASED LEFT VENTRICULAR EJECTION FRACTION

Decreased LVEF has been seen with cobimetinib (See Section 5.1.1.1) Refer to Table A3-6. Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption.

Left Ventricular Ejection Fraction (LVEF) Decrease From Baseline				
Patient	LVEF value	Recommended action with cobimetinib and atezolizumab	LVEF value following treatment break	Recommended cobimetinib daily dose
Asymptomatic	≥50% (or 40%–49% and<10% absolute decrease from BL)	Continue atezolizumab and cobimetinib at current dose	N/A	N/A
	<40% (or 40%–49% and≥10% absolute decrease from BL)	Interrupt cobimetinib treatment for 2 wk Continue atezolizumab as clinically indicated	<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	N/A		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

		Interrupt cobimetinib treatment for 4 wk. Consider withholding atezolizumab Discuss with Medical Monitor regarding resumption of atezolizumab. Cardiology consultation is strongly recommended.	Symptomatic regardless of LVEF	Permanent discontinuation

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

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE ELEVATED CPK

Elevated CPK has been reported with cobimetinib (see Section 6.1.2.5). See Table A3-7.

Table A3-7 Recommended Dose Modifications for Cobimetinib in Patients with CPK Elevations

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation	
General guidance	• Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
Asymptomatic CPK elevation, Grade 1, 2, or 3	• Continue atezolizumab and cobimetinib. • Recheck CPK at least once a week.
Asymptomatic CPK elevation, Grade 4	• Withhold cobimetinib and atezolizumab treatment. • If improved to Grade ≤ 3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. If not, permanently discontinue cobimetinib. • Resumption of atezolizumab may be considered in patients who are deriving benefit.
Rhabdomyolysis or symptomatic CPK elevations	• Withhold cobimetinib and atezolizumab treatment. • If event improves by at least one grade and symptoms resolve within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. If not, permanently discontinue cobimetinib. • Resumption of atezolizumab may be considered in patients who are deriving benefit after discussion with the Medical Monitor.
Hemorrhage	
Grade 3 hemorrhage other than cerebral hemorrhage	• Withhold cobimetinib. Continue atezolizumab. • Clinical judgment should be applied when considering whether cobimetinib should be resumed. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. • If cobimetinib cannot be resumed within 28 days, permanently discontinue cobimetinib.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Permanently discontinue cobimetinib if the event is attributed to cobimetinib; otherwise, withhold cobimetinib. Continue atezolizumab. • Clinical judgment should be applied when considering whether cobimetinib should be resumed. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events.

CPK = creatine phosphokinase.

Event	Action to Be Taken
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above	• Withhold atezolizumab and cobimetinib. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a,b,c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 7 Anaphylaxis Precautions

PRECAUTIONS

Equipment needed:

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

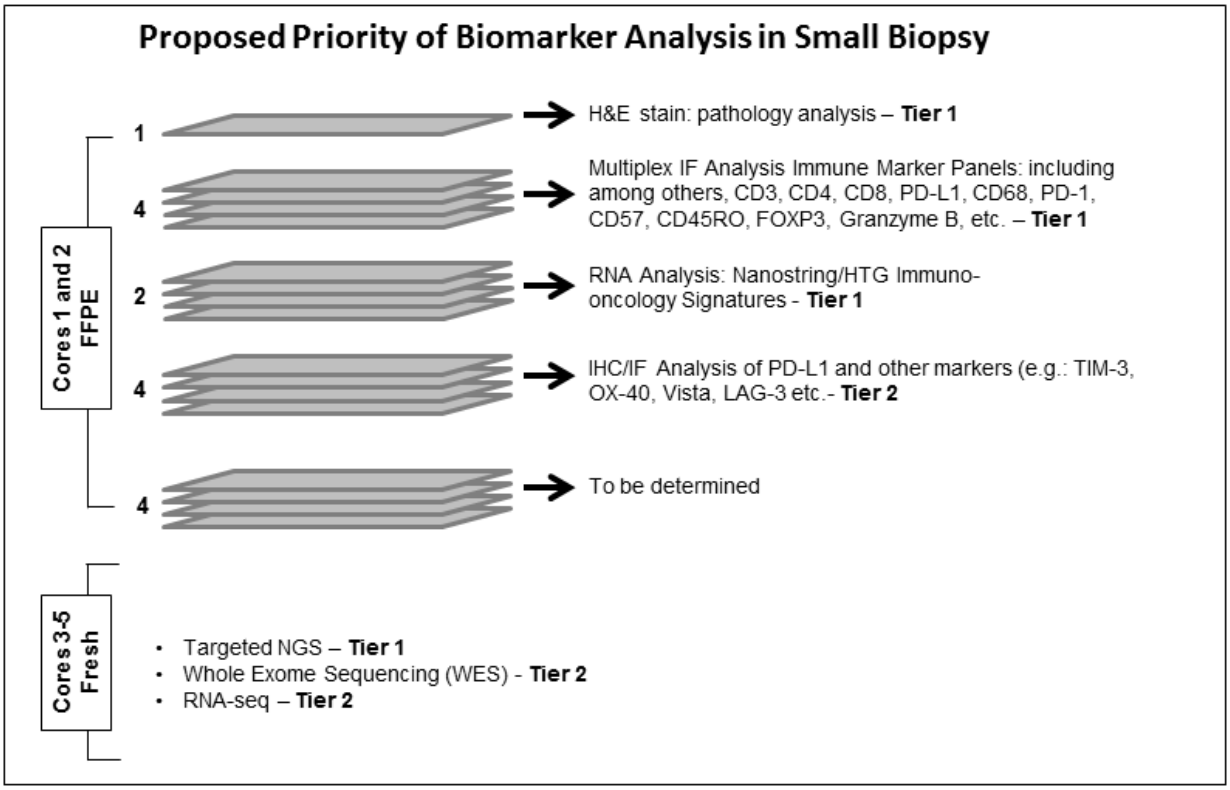
PROCEDURES

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

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

Appendix 8 Biomarker Analysis

- **Samples Collection and Processing:**
  - ***Core needle biopsy (CNB) or excisional biopsy:*** A fresh CNB or excisional biopsy will be obtained with the purpose of research studies before and after treatment and sent to the MD Anderson Institutional Tissue Bank (ITB) immediately after collection. At least 5 tissue cores will be obtained from the CNB/surgical procedure. The number of cores obtained will be affected by the patient clinical condition at the time of biopsy and determined by the radiologist who is performing the procedure. It is important to note that in some patients, the biopsy sample will also be required for clinical diagnosis. In such case, the first specimen will be prioritized for clinical specimen processing. In most instances, a rapid on site evaluation (ROSE) is available locally to evaluate the adequacy of clinical sample, thus additional biopsies may be procured for this research project. Nevertheless, the amount tissue available for correlative studies can be variable. Core biopsy is typically performed using 21-18 gauge needle and with condition permitting, up to 5 cores should be collected.
  - These cores/surgical excision pieces will be processed for (Figure 1):



Blood

- cfDNA – **Tier 3**
- Cytokines – **Tier 3**
- Exosome seq - **Optional**
- TCR repertoire analysis and flow cytometry panel - **Optional**.

- Cores or excision pieces 1 and 2: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples). The FFPE sample is important as it also provides a histological confirmation for the presence and cellularity of tumor cells. FFPE samples will also be prioritized for immune gene expression profiling by NanoString or other to be determined assays (Figure 1)
- Cores or excision pieces 3 to 5: Flash freezing in liquid nitrogen will be obtained for RNA (RNA-sequencing) and DNA (targeted or whole exome sequencing (WES), among other analysis. Potentially, flow cytometry from fresh tissue tumor tissues could be performed in selected cases.

- The tissue and blood will be processed as follows:
  - FFPE Tissues: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples). For pathology evaluation, at least one sample per 1-cm of diameter will be submitted for FFPE processing and pathology analysis. Hematoxylin and eosin (H&E)-stained sections from all FFPE diagnostic slides (tumor and adjacent normal level) will be scanned in Aperio image analysis for pathological evaluation and biomarker analysis
  - Fresh Tissues: Flash freezing in liquid nitrogen for genomic studies including RNA-sequencing and Whole Exome Sequencing (WES).
- ***Blood Specimens:*** 40 ml of blood will be collected at several time points (pre-treatment or baseline, cycle 1 day 15, and at the time of disease progression [+/- 1 week]) for:
  - Isolation of germ-line DNA from peripheral mononuclear blood cells (PMBCs) and TCR- T-cell receptor repertoire.
  - Isolation of plasma for cell free DNA analysis of genomic abnormalities using gene panels or analysis of cytokines associated with T-cell activation.
  - Isolation of circulating tumor cells (CTCs).
  - Potential flow cytometry analyses for phenotypic and functional studies.

- **Biomarker Analysis:**
  - ***Histology evaluation of tumor tissue:*** H&E-stained sections from CNBs and surgical excisions will be used to confirm the presence of tumor cells, as well as their abundance (tumor cellularity), stromal components and lymphocytic infiltrates. Hematoxylin and eosin (H&E)-stained sections from all FFPE diagnostic slides (tumor, normal and lymph nodes) will be scanned in Aperio™ digital pathology scanner analysis for pathological evaluation and selection of 1 or 2 blocks (depending on tumor availability) for biomarker analysis.

From the tumor tissue specimens, the following pathological analysis will be performed: 1) tumor diagnosis using the World Health Organization (WHO) classification; 2) lowest degree of tumor differentiation; 3) percentage of areas of necrosis; 4) percentage of areas of fibrosis; 5) percentage of viable tumor tissue; and, 6) percentage of viable malignant cells.

Central Review: The scanned H&E-stained slides will be available for pathology analysis at the Translational Molecular Pathology and Biomarker Lab chaired by Dr. Ignacio I. Wistuba, MD Anderson Cancer Center.

- ***Quality Control (QC) of tumor tissue:*** All tissue specimens collected will be reviewed by reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells; b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned and digital images will be available for review.
- ***Immunohistochemistry (IHC) and Immunofluorescence (IF) analyses:*** Fresh frozen and FFPE tissues will be used for analysis of immune markers. For immunohistochemistry (IHC) and multiplex immunofluorescence (IF) analyses, histology sections obtained from FFPE samples will be utilized (Figure 1). IHC and IF will be performed using autostainers. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software; IHC analysis will be performed using the Aperio Image Toolbox™ (Leica Biosystems) and IF analysis using, among pthers, the Vectra Inform™ (Perkin-Elmer) software. The following markers will be performed using optimized and validated protocols, as follows:
    - IHC assays: Staining of tumor tissue for PD-L1 will be conducted before and after treatment and be performed using the proper IHC assay. Briefly, 4µm-thick histology sections will be used for IHC will be performed on autostainers (Leica Bond Max, Leica Biosystems, Vista, CA). All antibodies have been optimized for IHC by examination of positive and negative controls and testing of the antibodies by Western blotting. To perform quantitative image analysis if the expression of each marker, all IHC slides will be scanned into a digital image scanner (Aperio™ AT Turbo, Leica Biosystems, Buffalo Grove, IL), and analyzed using the Aperio Image Genie Toolbox™ software (Leica Biosystems, Buffalo Grove, IL). Five random 1-mm square areas within the tumor region will be selected for analysis. The expression of IHC marker(s) in malignant cells will be evaluated using the Aperio™ digital H-score system which includes the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300. The expression of markers in

inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area.

- Multiplex IF Analysis: Up to 20 immune markers distributed in 3-4 panels will be utilized. For multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. The expression of protein markers and inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. The data and digital images will be deposited in a central database for review by pathologists. Among other markers, we will study the expression of the following CD3, CD4, CD8, PD-L1, PD-1, FOXP3, CD45RO, CD57, CD68, and Granzyme B; additional markers will be selected according the results of the gene expression analysis and may include other immunotherapy targets (e.g., OX-40, Vista, GITR, TIM-3, LAG-3, NKp46/CD16, etc.) and proliferation markers (e.g., Ki67).

- ***Nucleic acids and protein extraction:*** Blood (plasma and PMBCs), tumor (CNB and surgical excision specimens) samples will be subjected to DNA, RNA and protein extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses. Also, protein lysate will be extracted using standard methods.
- ***Molecular analysis of tumor tissues:*** Using FFPE and/or fresh frozen for CNBs/surgical excisions (Figure 1), the following analysis will be performed:
  - Immuno-oncology (IO) gene expression signatures: Using FFPE tumor tissues, IO panels of genes will be examined using the Nanostring technology (nCounter). This assay will be used to measure expression levels of drug targets, tumor infiltrate composition, and total immune cell composition using a single section of FFPE tumor tissue. The Nanostring methodology offers a cost-effective way to analyze the expression levels of up to 800 genes simultaneously, with precision superior to qPCR. The current Nanostring PanCancer Immune Profiling Panel includes 770 genes and combines markers for 24 different immune cell types and populations, 30 common cancer antigens and genes that represent all categories of immune responses including key checkpoint blockade genes. Alternatively, we will apply the HTG Edge Seq technology, also known as quantitative nuclease protection assay or HTG Edge Chemistry that enables extraction and amplification-free quantitation of mRNA from FFPE tissues without RNA extraction. Their Immuno-Oncology Assay examines the expression of 549 genes implicated in the host immune response to tumors.
  - Next Generation Sequencing (NGS) analysis: To study tumor molecular abnormalities, fresh, and alternatively, FFPE tumor tissues before and after treatment will be examined for targeted gene panel NGS (analysis of mutations, copy number, indels, translocations), whole exome sequencing

(WES) and RNA sequencing. Targeted NGS: Different sequencing platforms can be used to sequence DNA extracted from clinical samples. These platforms have a minimum input of 10ng of sample which make it amenable to sequencing with minimal DNA. The panels available are, among others, CMS50, CMS400, Oncomine and Foundation Medicine. They range from 50 to 409 oncogenes and tumor suppressor genes, with coverage of hotspots and whole exomes. All these platforms are available at facilities at MD Anderson Cancer Center. WES and RNA-seq: Illumina Hi-seq platform is available at the Sequencing Facilities at MD Anderson Cancer Center

- ***Flow cytometry Analysis:*** This type of analysis may be applied to two types of specimens.
  - Cryopreserved PBMCs**:** High order flow cytometry panels are available for analysis of tumor tissue and blood specimens. The panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ, TNFα, GB) and 3) defining the expression level of costimulatory and co-inhibitory molecules on T cells. The proposed studies may be conducted retrospectively on cryopreserved PBMCs. Briefly, 40 cc of heparinized peripheral blood from patients prior to the initiation of treatment, and at 3 time points throughout treatment (2 weeks, 8 weeks and at time of progression) will be processed fresh (within 24h of being drawn) for PBMC isolation. PBMCs will be cryopreserved and stored in liquid nitrogen until use.
  - Flow cytometry of freshly disaggregated tumor tissue. In selected cases, fresh tissue will be available for flow cytometry analysis. Tumor tissue will be stored in HBSS for up to 24h before processing for flow cytometry. Fresh tissue will be mechanically disaggregated or digested according to needs and panel design. The cells will be processed as a single cell suspension and stained according to each customized panel.
- ***Liquid biopsy analysis:*** Liquid biopsies are non-invasive blood tests that detect tumor cell free DNA (cfDNA) that are shed into the blood from the primary tumor and from metastatic sites. cfDNA testing offers the opportunity to take serial samples in order to monitor tumor genomic changes in real time. There are several platforms available at MD Anderson Cancer Center, including the application of droplet digital PCR (ddPCR) platform in a small panel of hot spots/genes or a larger panel of genes using NGS platform. Additionally, isolation of circulating tumor cells (CTCs) and exosomes for genotyping DNA purposes are available as optional analysis of blood compartments.
- ***TCR receptor repertoire***: TCR sequencing analysis may be performed using DNA from tumor tissues as well as PBMC. Briefly, 500 ng tumor DNA or 3-6 ug PBMC DNA will be subjected to high throughput TCR Vβ CDR3 sequencing on an Illumina HiSeq sequencer with at least 5-fold coverage by ImmunoSEQ™ sequencing (Adaptive Biotechnologies, Seattle, WA). TCR profile generated from treatment-refractory

tumors at the time of disease progression will be compared to data from pre-treatment tumor samples to explore the TCR repertoire evolution of these tumors under therapeutic pressure. The dynamic changes of TCR from PMBC, when longitudinal blood samples are available, will be correlated to response to immune checkpoint blockade or chemotherapy and survival.

- ***Cytokines analysis***: For the detection of soluble factors in plasma we may use the SQ120 instrument from Meso Scale Discovery (MSD). This and other technologies allow for the detection of up to 40 analytes per well and uses a very low sample volume, with a sensitivity up to 1000 fold higher than traditional ELISA assays with a large linear range of 3-4 logs. These technologies can be utilized for either single agent detection or in multiplex format.