Date: February 26, 2025

To: CTEP Protocol and Information Office

From: [redacted], MD

Study: 10166 *A Phase 2 Study of Atezolizumab and Cobimetinib in PD-1/PD-L1 Inhibitor Resistant or Refractory Non-Small Cell Lung Cancer*

Re: Amendment in response to a RRA from Dr. [redacted] dated 02/24/2025, RA from CTEP dated 10/1/2024, and changes from CTEP dated 3/6/2025.

SUMMARY OF CHANGES – Protocol

I. In Response to the Request for Rapid Amendment from Dr. [redacted] dated 2/24/25:

#	Section	Comments
1.	Header, Title Page	Updated protocol version.
2.	Throughout	Updated language as requested by CTEP.
3.	7.1.1.1	In response to the RRA from Dr. [redacted] dated 02/24/2025, the CAEPR for Atezolizumab has been replaced with version 2.5 dated 11/18/2024. The following change was made: • Added New Risk: • Rare but Serious: Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia); Endocrine disorders - Other (thyroiditis); Rhabdomyolysis; Vascular disorders - Other (immune-mediated vasculitis)
4.	7.3.3	Updated the AE Expedited Reporting Tables for Phase 1 and Early Phase 2 Studies to version August 30, 2024.

II. In Response to the Request for Amendment from CTEP dated 10/1/24:

#	Section	Comments
5.	9.5.1.4	Changed the shipping address to: EET Biobank 2200 International Street

#	Section	Comments
		Columbus, OH 43228 PH: (614) 722-2865 FAX: (614) 722-2897 E-mail: BPCBank@nationwidechildrens.org
7.	9.5.1.5	Updated the contact information to: EET Biobank PH: (614) 722-2865 E-mail: BPCBank@nationwidechildrens.org

III. In Response to the Request from CTEP dated 3/6/2025:

#	Section	Comments
8.	9.8.7.2	In Section 9.8.7.2 (cfDNA) revise the Site Performing Correlative Study text to: The Broad Institute (address below), working with ~~Mount Sinai~~ CIMAC , will perform the cfDNA analyses. ~~Broad Institute Genomics Services~~ ~~320 Charles Street~~ ~~Cambridge, MA 02141~~ The Broad Institute Attn: Samples Lab 27 Blue Sky Drive Burlington, MA, 01803
9.	9.9	In the Biomarker Table (Section 9.9.) revise the lab for the following biomarkers as shown: • For both tissue and blood-based TCRseq, change "Mt. Sinai CIMC via Adaptive" to "Adaptive in collaboration with CIMAC" • For cfDNA, change "Mt. Sinai CIMAC via The Broad Institute" to "The Broad Institute in collaboration with CIMAC"

SUMMARY OF CHANGES – Consent Form

#	Section	Comments
1.	Header	Updated protocol version.

2.	Possible Side Effects of Atezolizumab	Revised risk information of Atezolizumab due to a RRA from Dr. [redacted] dated 2/24/2025. The following changes were made to the risk table:
		• Added New Risk:
		  • Rare and Serious: Swelling or tenderness of blood vessels
		• Provided Further Clarification:
		  • Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine, previously reported (under Rare) is now reported as, Problem of the muscle (myositis, rhabdomyolysis), including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Rare)

NCI Protocol #: 10166

Local Protocol #: TBD

ClinicalTrials.gov Identifier: NCT03600701

TITLE: A Phase 2 Study of Atezolizumab and Cobimetinib in PD-1/PD-L1 Inhibitor Resistant or Refractory Non-Small Cell Lung Cancer

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NCI-Supplied Agents: Atezolizumab NSC # 783608
Cobimetinib NSC # 781257

IND#: [redacted]
IND Sponsor: DCTD; NCI

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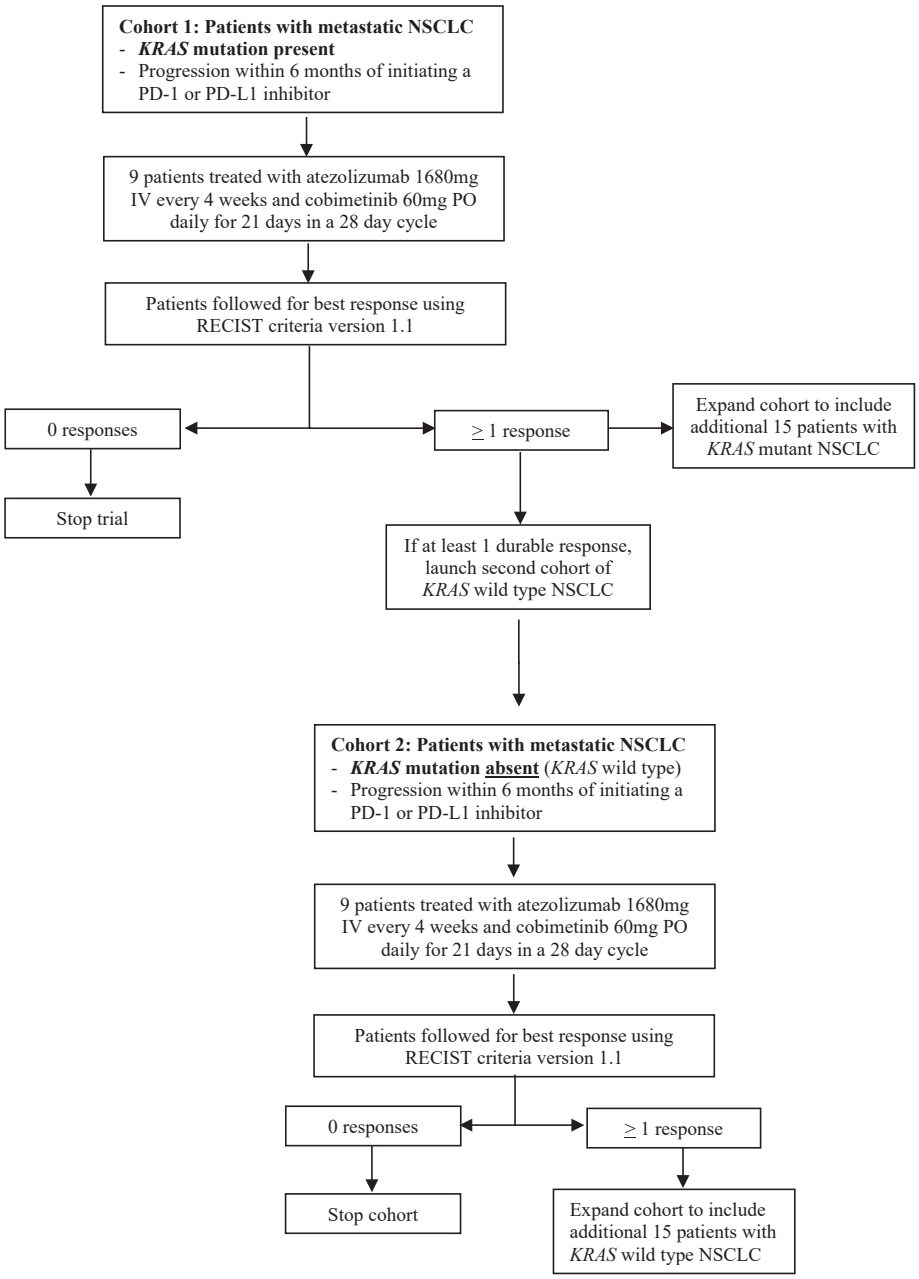
Revised / Amendment 19 / 26 February 2025

SCHEMA



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1. OBJECTIVES

1.1 Primary Objectives

To evaluate durable overall response rate with atezolizumab plus cobimetinib in patients with metastatic non-small cell lung cancer (NSCLC) resistant or refractory to prior PD-1 or PD-L1 therapy.

1.2 Secondary Objectives

1.2.1 To evaluate the overall response rate of atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy

1.2.2 To evaluate the progression-free survival (PFS) of atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy

1.2.3 To evaluate the overall survival (OS) of atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy

1.2.4 To evaluate the duration of response (DOR) of atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy

1.2.5 To evaluate the grade 3 and 4 toxicity rate in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy when treated with atezolizumab plus cobimetinib

1.3 Exploratory Objectives

1.3.1 To evaluate the consequences of treatment with atezolizumab plus cobimetinib on the tumor microenvironment in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy

1.3.2 To correlate genomic characteristics including tumor mutation burden to response to therapy with atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy

2. BACKGROUND

2.1 NSCLC

The implementation of checkpoint inhibitors for the treatment of advanced non-small cell lung cancer (NSCLC) has been one of the most impactful developments in decades. Two PD-1 inhibitors, pembrolizumab and nivolumab, and one PD-L1 inhibitor, atezolizumab, are approved following chemotherapy for NSCLC. Pembrolizumab, atezolizumab, and cemiplimab have also been approved as first-line monotherapy for patients whose tumors highly express PD-L1; nivolumab plus ipilimumab are approved for tumors with any PD-L1 expression, and pembrolizumab, atezolizumab and the combination of nivolumab and ipilimumab are approved when given with chemotherapy, independent of PD-L1 status (Herbst *et al.*, 2021). A well tolerated alternative to chemotherapy, use of PD-1 and PD-L1 inhibitors has demonstrated the potential for meaningful, durable disease control – an outcome not expected with standard cytotoxic therapy. PD-1 and PD-L1 inhibitors have transformative potential with impressive durations of response and long term control for a subset of patients. Unfortunately, long term survival rates remain modest. While salvage chemotherapy can be considered, patients with NSCLC unresponsive to a checkpoint inhibitor need better treatment options.

This is particularly true for the subset of patients whose tumors harbor a mutation in *KRAS*. *KRAS* mutations are one of the most common genomic alterations identified in NSCLC, present in about 25% of cases and historically, these tumors have been less responsive to therapy. In particular, presence of *KRAS* mutations is mostly reciprocally exclusive of actionable mutations, such as *EGFR* mutations and *ALK* or *ROS1* translocations. Sotorasib has been approved for patients whose tumors harbor KRAS G12C mutations and while they offer improvements in PFS over standard second line chemotherapy, there was not an improvement in survival (Johnson *et al.*, 2022). In the randomized phase III trial comparing nivolumab to docetaxel in non-squamous cell carcinomas, the subset of patients with a *KRAS* mutation had better outcomes with nivolumab, though overall response rates remain low (Borghaei *et al.*, 2015). *KRAS* mutations are mainly present in adenocarcinoma patients and are highly associated with cigarette smoking; exposure to cigarette smoke is known to be associated with a higher mutational burden and therefore potentially a better response to immune checkpoint inhibitors (Rizvi *et al.*, 2015). Because *KRAS* mutations constitutively activate the RAF-MEK-ERK pathway, inhibition of MEK has been explored in *KRAS* mutant NSCLC. The addition of the MEK inhibitor selumetinib to docetaxel improved progression free survival and response in a randomized phase II study but there was not a significant difference in a phase III trial (Janne *et al.*, ESMO 2016). Alternative strategies remain a pressing need.

2.2 CTEP IND Agents

2.2.1 Atezolizumab

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells (Investigator's Brochure v10, July 2017). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid

substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits the interaction with its PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.

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

Atezolizumab is approved in the United States for the treatment of metastatic non-small cell lung carcinoma.

2.2.1.1 Mechanism of Action

PD-L1 expression is prevalent in many human tumors (*e.g.*, lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (Thompson *et al.*, 2006; Hamanashi *et al.*, 2007; Okazaki and Honjo 2007; Hino *et al.*, 2010). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1), and receptor expression is sustained 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 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition 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 and PD-L1/B7.1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Blockade of PD-L1 or PD-1 with monoclonal antibodies has been reported to result in strong and often rapid antitumor effects in several mouse tumor models (Iwai *et al.*, 2002; Strome *et al.*, 2003). These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or inhibited state, and blockade of the PD-L1/PD-1 pathway can reinvigorate tumor-specific T-cell responses.

Collectively, these data establish the PD-L1/PD-1 pathway as a promising new therapeutic target in patients with advanced tumors. Immune-related adverse events (AEs) reported from the two recent studies were consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance.

2.2.1.2 Summary of Nonclinical Experience

The safety, pharmacokinetics (PK), 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. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed phase 1 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 trials in patients.

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

2.2.1.3 Summary of Clinical Experience

A summary of clinical data from company-sponsored atezolizumab trials is presented below. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

2.2.1.3.1. Clinical PK and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab shows linear PK at doses ≥1 mg/kg (Investigator's Brochure v10, July 2017). Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21−89 years), body weight, sex, positive ATA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status. No formal PK drug-drug interaction studies have been conducted with atezolizumab, and the interaction potential is unknown. Further details can be found in the current Investigator's Brochure.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg) (Investigator's Brochure, 2016). Patients dosed at ≥10 mg/kg maintained C_{min} values well above the target serum concentration of 6 mcg/mL despite the detection of ATAs. Accordingly, the development of detectable ATAs does not appear to have a clinically significant impact on PK for doses above 10 mg/kg. To date, no relationship between the development of measurable ATAs and safety or efficacy has been observed.

2.2.1.3.2. Clinical Safety Summary

As of May 10, 2016, atezolizumab has been administered (alone or in combination with other agents) to approximately 6053 patients with solid tumors and hematologic malignancies (Investigator's Brochure v10, July 2017). The first-in-human monotherapy study PCD4989g (in patients with locally advanced or metastatic solid tumors or hematologic malignancies) provides the majority of monotherapy safety data, with 629

safety-evaluable patients as of the data extraction date. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of AEs have been determined.

Fatigue, decreased appetite, nausea, diarrhea, constipation, and cough were commonly reported AEs in single and combination therapy (Investigator's Brochure, 2016). AE profiles are similar across tumor types studied, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma (UC), and are consistent with the mechanism of action of atezolizumab. The overall immune-mediated AEs reported were considered moderate in severity, and the majority of patients were able to continue on atezolizumab therapy.

As of the data extraction date of December 15, 2015, there were 629 safety-evaluable patients from the first-in-human phase 1a study PCD4989g (Investigator's Brochure, 2016). The median age was 61 years. Of the 629 patients, 619 patients (98.4%) reported at least one AE of any grade or attribution to atezolizumab, and 316 patients (50.2%) experienced at least one grade 3 or 4 AE of any attribution. A total of 444 patients (70.6%) reported at least one treatment-related AE, and 86 patients (13.7%) experienced at least one treatment-related grade 3 or 4 AE. The most frequently observed AEs of any grade and attribution (occurring in ≥10% of treated patients) include fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema, and dizziness.

Serious AEs (SAEs) have been reported in 261 patients (41.5%) in study PCD4989g (Investigator's Brochure, 2016). Reported SAEs were consistent with the underlying disease. Treatment-related SAEs (57 patients [9.1%]) included pyrexia, dyspnea, pneumonitis, malaise, fatigue, hypoxia, colitis, and bone pain. Pooled single-agent safety data from 1978 patients with UC, NSCLC, and other indications (including trial PCD4989g) indicate that the most frequent (>1% of patients) serious adverse drug reactions (regardless of grade) include dyspnea (3.0%), back pain (1.2%), and abdominal pain (1.1%). A list of AEs considered "expected" for atezolizumab is presented in Section 7.1.1.1.

2.2.1.3.3. Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program (Investigator's Brochure, 2016). To date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

For further details, see the most recent Atezolizumab Investigator's Brochure.

2.2.1.3.4. Clinical Efficacy Summary

Patients with multiple tumor types were included in study PCD4989g, with the largest cohorts consisting of patients with NSCLC, RCC, and UC (Investigator's Brochure, 2016). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UC, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Both the preliminary and more mature efficacy data available suggest that treatment with atezolizumab as a single agent or in combination with other therapeutic agents results in anti-tumor activity across a range of tumor types and hematologic malignancies (UC, NSCLC, RCC, TNBC, melanoma, CRC, and NHL) and across lines of therapy. Clinical benefit was observed in terms of objective responses, durability of responses, and overall survival (OS). Improved efficacy of atezolizumab was observed in the unselected patient population, as well as in patients with higher PD-L1 expression on TCs or ICs (*e.g.*, NSCLC) or on ICs only (*e.g.*, mUC, RCC).

2.2.2 Cobimetinib

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.

2.2.2.1 *Summary of Nonclinical Studies with Cobimetinib*

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.

2.2.2.2 *Summary of Clinical Studies with Cobimetinib Monotherapy*

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.

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%]).

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.

For further clinical information on cobimetinib as monotherapy or with other anti-cancer agents, please see the cobimetinib Investigator's Brochure.

2.3 Other Agents

Not applicable.

2.4 Rationale

2.4.1 Rationale for combination

NSCLC tumors can be refractory to immune checkpoint inhibition for numerous reasons and it has become increasingly clear that the tumor microenvironment plays a critical role in mediating or permitting an antitumor immune response. Preclinical studies have shown that inhibition of MEK has a potentially relevant impact on the tumor microenvironment, promoting accumulation of T-cells in the tumor and upregulating MHC class I molecules. There has been preclinical support of synergy between MEK inhibition and PD-L1 blockade (Ebert *et al*., 2016), with an

increase in T-cell infiltration of the tumor following use of the MEK inhibitor cobimetinib. Based on these data, a study combining cobimentinib and atezolizumab was launched. The combination was well tolerated (Bendell *et al*., ASCO 2016). Atezolizumab was given at a dose of 800mg every 2 weeks and cobimetinib was given daily at doses of 20mg, 40mg and 60mg. No dose limiting toxicities were noted and the dose of 60mg has moved forward in subsequent trials, based largely on the promising results seen in colorectal cancer. Patients were heavily pretreated with a median of 3 prior lines of therapies and all patients received prior oxaliplatin and irinotecan. In 23 patients, the response rate was 17%. In *KRAS* mutant colorectal cancer (n=20), the response rate was 20%. Three of the 4 responses were in MSI-low or stable colorectal cancer). While there was no control arm of atezolizumab alone, non-MSI-high colorectal cancer has not consistently demonstrated meaningful response to PD-1 inhibition and the results seen here led to a randomized study currently underway.

With early evidence that MEK inhibition can promote responses to PD-L1 inhibition in what has been an immunotherapy-refractory disease, we propose to explore the addition of MEK inhibition to immunotherapy refractory NSCLC, i.e. patients who have received a PD-1 inhibitor such as nivolumab or pembrolizumab in the advanced setting and did not achieve a response. We propose a single-arm, Simon two-stage phase II study of cobimetinib plus atezolizumab in patients with NSCLC unresponsive to prior PD-1 inhibition. As MEK inhibition may have additional therapeutic benefit in *KRAS* mutant NSCLC, this combination will first be explored in a cohort of patients with *KRAS* mutant NSCLC. If sufficient activity is seen in this subgroup, the combination will then be explored in a separate cohort with *KRAS* wild type NSCLC. The hypothesis is that concurrent use of a MEK inhibitor will increase infiltration of CD8+ T-cells into the tumor to improve efficacy of the PD-L1 inhibitor and correlative tissue studies will be used to demonstrate the immunologic consequences of concurrent therapy.

2.4.2 Rationale for dose

In Arm A (cobimetinib plus 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 every2 weeks has the equivalent dose exposure as the 1200 mg every 3 weeks (21–day cycle), the planned dose for the atezolizumab monotherapy arm. 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 was initially selected in this study to simplify dose administration.

More recently, a 1680 mg dose given every 4 weeks was FDA approved. This dosing schedule is expected to have comparable efficacy and safety compared to the 1200 mg every 3 weeks or 840 mg every 2 weeks schedules (Morrissey *et al*., Cancer Chemother Pharmacol 2019). For dosing convenience and to minimize infusion visits, the protocol was modified to adopt an atezolizumab schedule of 1680 mg every 4 weeks.

2.4.3 Rationale for study design

Initially, the study will include only patients with NSCLC harboring a *KRAS* mutation. This testing can be done by any CLIA certified laboratory and will not require central confirmation. If this cohort is positive in that it meets its primary endpoint (see section 13.2), a second cohort may open exploring the combination in patients whose tumor does not harbor a *KRAS* mutation (*KRAS* wild type). However, in order for the second cohort to open, at least one durable response must be seen. This is defined as a confirmed partial response in a patient treated for at least 6 months. Cobimetinib may induce transient responses in *KRAS* mutant NSCLC via MEK inhibition and independent of its impact on T-cell infiltration. These responses would be transient. A durable response lasting at least 6 months is much more likely to be immune mediated. Thus, to justify opening a cohort in *KRAS* wild type NSCLC, at least one durable response must be seen among the required number of responses outlined in section 13.2.

2.5 Correlative Studies Background

While immunotherapy has proven to be a transformative treatment for some patients, with no patient selection the majority of patients with NSCLC will not respond to checkpoint inhibitors. Development of an appropriate predictive biomarker is critical to proper delivery of patient care. Understanding immune escape mechanisms and the underlying biology of primary resistance to checkpoint inhibitors will also improve delivery of care. This study provides a valuable opportunity to gain insight into factors promoting or preventing response. All patients will be required to undergo a research biopsy prior to starting therapy and upon completion of cycle 1. There is also an optional research biopsy at progression. In addition, when available, archived specimens will be collected from baseline biopsies taken prior to the patients' initial treatment with a checkpoint inhibitor. Blood will also be collected for analysis (see Study Calendar, Section 10).

2.5.1 Changes in tumor infiltrating lymphocytes following treatment with atezolizumab plus cobimetinib

Evidence suggests that pre-existing tumor-associated CD8+ T-cells can determine response to anti-PD-1 therapy in patients with melanoma. Tumeh *et al.* used qualitative and quantitative immunohistochemistry analysis for CD8 expression before and after PD-1 blockade in patients with melanoma (Tumeh *et al*., 2014). Patients who experienced a response to therapy showed higher CD8+ cell densities at the invasive margin compared to patients who progressed on therapy. In patients with delayed responses, CD8+ cells accumulated in a step-wise fashion. A greater increase in CD8+ cell density corresponded with a decrease in tumor size. To show a correlation with interferon production, phospho-STAT1 was also tested and higher expression at the margin was seen in patients who achieved response (compared to progression).

This study explores the combination of MEK inhibition with cobimetinib and PD-L1 blockade with atezolizumab. In preclinical models, MEK inhibition with cobimetinib led to an increase in T-cell infiltration (Ebert *et al*., 2016). Here, we will seek to confirm T-cell infiltration (specifically, CD8+ T-cell infiltration) increases with use of cobimetinib. Patients will undergo a biopsy prior to treatment and after 1 cycle (4 weeks) of treatment. Using multiplex IHC, we will

then compare CD8+ infiltration before and during therapy, anticipating an increase in CD8+ T-cell infiltration with the use of cobimetinib. To assess the architecture of these lymphocytes, we will also submit one slide for H&E staining.

Past studies have demonstrated that multiplex immunohistochemistry with either chromogenic or immunofluorescence detection can be used to identify and quantitate individual marker specific immune and tumor cell populations, as well as their spatial relationships (Gibney *et al*., 2016). This provides a more detailed immune characterization of the tumor microenvironment and up to eight markers can be detected using immunofluorescence and multispectral imaging, depending on the platform used. Tumeh et al. showed that spatial interaction of immune cell PD-1 with tumor cell PD-L1 was associated with response to anti-PD-1 therapy in patients with advanced melanoma (Tumeh *et al*., 2014). Furthermore, use of multiplex IHC has been demonstrated to predict successful TIL growth from melanoma tumors for adoptive cell therapy – in particular tumors with a high CD8+ T cell to CD3+FoxP3+ regulatory T-cell ratio (Feng *et al*., 2015).

Gene expression analysis has been utilized to contextually evaluate immune biomarkers and identify signatures associated with immune escape and response to therapy (Chen and Mellman, 2017). In NSCLC, atezolizumab improved overall survival in patients with tumors characterized by high expression of T-effector-associated and interferon-y-associated genes (HR 0.45; 95% CI 0.24-0.77) (Fehrenbacher *et al*., 2016). RNA sequencing on tissue samples obtained prior to atezolizumab and cobimetinib therapy and, if available, also prior to anti-PD1 therapy and at disease progression, we aim to study changes and dynamics in the immune cell subsets over time and investigate them in the context of clinical outcome.

2.5.2 Genomic determinants of response to immunotherapy

A growing body of evidence in NSCLC supports a relationship between the genomic characteristics of a tumor and likelihood of response to checkpoint inhibitors. Rizvi *et al.* performed exome sequencing of patients with NSCLC treated with pembrolizumab (Rizvi *et al.*, 2016). In these analyses, higher somatic nonsynonymous mutation burden was associated with clinical benefit to pembrolizumab. Patients with a mutation burden above the median had a higher response rate (63% vs. 0%) and longer PFS (HR 0.19, 95% CI 0.05-0.70). The specific mutations may also be relevant. Specific defects in the interferon-receptor signaling pathway such as mutations in Janus kinase 1 or 2 (*JAK1*, *JAK2*) have been associated with acquired resistance to PD-1 inhibitors (Zaretsky *et al.*, 2016).

Here, we will perform whole exome sequencing on tissue samples obtained prior to atezolizumab and cobimetinib therapy to further explore a relationship between mutational profile and response. Furthermore, we will explore on paired tissue samples obtained prior to anti-PD1/-PD-L1 therapy changes in mutational burden and will assess neoantigens. Neoantigen expression will be confirmed using RNA sequencing.

Whole blood will be collected at baseline, at the start of cycle 2 and at the end of treatment. Blood will be analyzed for changes in markers of immune cell populations, including, but not limited to, markers for immune cell populations (CD3+, CD4+, and CD8+ T lymphocytes; Tregs).

3. PATIENT SELECTION

3.1 Eligibility Criteria

All answers must be 'Yes' to be eligible.

3.1.1 Patients must have histologically or cytologically confirmed metastatic or recurrent non-small cell lung cancer (any histology is permitted).

Presence of a mutation in *KRAS* as detected by a CLIA-approved assay is required for patients enrolled in cohort 1. Central validation is not required for enrollment.

Absence of a mutation in *KRAS* (*KRAS* wild type) is required for patients enrolled in cohort 2. Central validation is not required for enrollment but *KRAS* mutation status must be known, regardless of histology.

3.1.2 Patients must have primary resistance to anti-PD-1 or anti-PD-L1 therapy, given as monotherapy or in combination with other agents. Patients must have experienced progressive disease within 6 months (180 days) of initiating treatment with a PD-1/PD-L1 inhibitor.

Anti-PD-1 or anti-PD-L1 therapy does not need to be the most recent therapy prior to study enrollment.

3.1.3 Patients with a sensitizing alteration in *EGFR*, *ALK* or *ROS1* are eligible provided they have experienced disease progression or intolerance to treatment with an approved EGFR, ALK or ROS1 inhibitor, respectively. Patients who have received investigational inhibitors may be eligible following discussion with the study PI.

3.1.4 Patients must have disease amenable to core biopsy and be willing to undergo the required research biopsies.

3.1.5 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.6 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of atezolizumab in combination with cobimetinib in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.7 ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A).

3.1.8 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥2,500/mcL
– absolute neutrophil count	≥1,000/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥ 8 g/dL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN) (however, patients with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)
– AST(SGOT)/ALT(SGPT)	≤3 × ULN (AST and/or ALT ≤5 × ULN for patients with liver involvement)
– alkaline phosphatase	≤2.5 × ULN (≤5 × ULN for patients with documented liver involvement or bone metastases)
– creatinine clearance	≥30 mL/min/1.73 m^2 by Cockcroft-Gault: $\frac{(140 - age) \times (weight\ in\ kg) \times (0.85\ if\ female)}{72 \times (serum\ creatinine\ in\ mg/dL)}$
– INR and aPTT ≤1.5 × ULN	(This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation, such as low-molecular-weight heparin or warfarin, should be on a stable dose.)

3.1.9 Administration of atezolizumab or cobimetinib may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of study agent. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.1.11 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2 Exclusion Criteria
All answers must be 'No' to be eligible.

3.2.1 Patients who have not recovered from clinically significant adverse events (other than alopecia) due to prior anti-cancer therapy.

3.2.2 Treatment with any investigational agent within 4 weeks prior to Cycle 1, Day 1.

3.2.3 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

- Patients who have received acute, low dose, systemic immunosuppressant medications (*e.g.*, a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.2.4 Patients with symptomatic CNS metastases are excluded

- Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
  - No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1
- Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No stereotactic radiation or whole-brain radiation within 28 days prior to Cycle 1, Day 1
  - Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

3.2.5 Has a known concurrent malignancy that is expected to require active treatment within two years, or may interfere with the interpretation of the efficacy and safety outcomes of this study in the opinion of the treating investigator. Superficial bladder cancer, non-melanoma skin cancers, or low grade prostate cancer not requiring therapy should not exclude participation in this trial.

3.2.6 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to atezolizumab or cobimetinib.

History of congenital long QT syndrome or corrected QT interval (QTc) by Fridericia Formula >450 msec within 28 days of Cycle 1, Day 1.

3.2.8 Cardiac ejection fraction below institutional LLN or below 50%, whichever is lower, as determined by echocardiogram or MUGA scan within 4 weeks of Cycle 1, Day 1

3.2.9 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.

3.2.10 Any Grade 3 or above hemorrhage or bleeding event within 4 weeks prior to initiation of study treatment.

3.2.11 History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to initiation of study treatment.

3.2.12 Patients receiving any medications or substances that are strong or moderate inhibitors or inducers of CYP3A4 enzymes are ineligible. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor). Because the lists of these agents are constantly changing, it is important to regularly consult medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.13 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.

- 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) <u>are eligible</u>.
- Patients positive for hepatitis C virus (HCV) antibody <u>are eligible only if</u> polymerase chain reaction (PCR) is negative for HCV RNA.

3.2.14 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, autoimmune hemolytic anemia, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
- 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)

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

3.2.16 Any significant active infection requiring treatment within 14 days prior to cycle 1, day 1

3.2.17 Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.

3.2.18 Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of atezolizumab.

- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

3.2.19 Uncontrolled pleural or pericardial effusion or ascites requiring recurrent drainage procedures.

3.2.20 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, active tuberculosis (TB), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.21 Pregnant women are excluded from this study because both atezolizumab and cobimetinib are expected to cause fetal harm if used during pregnancy. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cobimetinib or atezolizumab, breastfeeding should be discontinued if the mother is treated with either therapy. These potential risks may also apply to other agents used in this study.

3.2.22 Inability or unwillingness to swallow pills.

3.2.23 History of malabsorption syndrome or other condition that would interfere with enteral absorption.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. However, pregnant women are excluded from this study because the study treatment may cause fetal harm if used during pregnancy.

In accordance with the NIH guidelines on the inclusion of women and minorities as subjects in clinical research, the NIH requires that all NIH defined clinical research studies must include planned enrollment. Below is the expected accrual over the life of the study.

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.
The accrual targets based on data from similar trials completed by our organization during the previous 5 years will resemble the sex, ethnic, and racial composition of the U.S. population as closely as possible. A complete description of ethnic and racial categories table will be filled as follows:

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	6	5	0	0	11
White	16	15	1	1	33
More Than One Race	0	0	0	0	0
Total	24	22	1	1	48

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4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR *Help Desk* by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI #10166 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select LAO-MD017, and NCI Protocol #10166.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For NCI #10166 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Internal site initiation visit (SIV) conducted by the site study PI with the site research team
  - SIV checklist and sign-in sheet must be completed and signed by site study PI and sent back to the Protocol Liaison of the lead LAO.
- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU.
  - This training will need to be completed before the first patient enrollment at a given site.
  - [redacted] and [redacted] are the main points of contact at Theradex for the training ([redacted] and [redacted], Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 Special Instructions for Patient Enrollment

The following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements: Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	*Premedications; Precautions*	*Dose*	*Route*	*Schedule*	*Cycle Length*
Atezolizumab	Premeds are not permitted for the first infusion. If patient experienced an Infusion-Related Reaction (IRR) during any previous infusion, pre-medication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician.	1680 mg	IV over 60 (± 15) min. If the patient tolerated the first infusion well without infusion-associated AEs, subsequent infusions may be delivered over 30 (± 10) min.	Day 1	28 days (4 weeks)
Cobimetinib	Cobimetinib should be taken at the same time every morning. It can be taken with or without food.	60 mg (three tablets, 20 mg each)	PO	Days 1-21	

The patient will be requested to maintain a medication diary of each dose of cobimetinib. The medication diary will be returned to clinic staff at the end of each course.

5.1.1 Atezolizumab

Atezolizumab has the potential to cause infusion reactions.

For anaphylaxis precautions, see the management guidelines. Atezolizumab infusions will be administered per the instructions outlined in the table below.

Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the

• Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

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

1. Stop the study drug infusion.
2. Call for additional medical assistance.
3. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.
6. Draw serum/plasma samples for immunogenicity testing.
7. Ask participant to return for washout immunogenicity sample if appropriate.

5.1.2 Cobimetinib

Cobimetinib should be taken at the same time every day. It can be taken with or without food. If a dose of cobimetinib is not taken within 1 hour of the scheduled dose, it should be considered missed and not taken. Resume dosing at the next scheduled dose. If vomiting occurs when the dose is taken, resume dosing with the next scheduled dose.

Patients receiving cobimetinib will be requested to maintain a medication diary (see Appendix D) of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. The study team should review the diary for completeness and any inconsistencies and discuss them with the participant at the visit.

5.2 General Concomitant Medication and Supportive Care Guidelines

Concomitant medication guidelines for atezolizumab and cobimetinib are provided below.

Because there is a potential for interaction of cobimetinib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions, including medications or substances that are inhibitors or inducers of CYP450 enzymes. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) for the assigned treatment arm should be provided to each participant.

5.2.1 General Concomitant Medication Guidelines for All Participants

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.
Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine 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 β_2-adrenergic agonists; see Section 5.1.1).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the patient is

enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin, warfarin at a stable dose level, or a non–vitamin K antagonist oral anticoagulants), should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

5.2.2 Excluded Therapies for Patients Receiving Atezolizumab

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited unless it is specifically included in the treatment regimen described in this protocol. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.
    - After completion of Cycle 1, external beam radiotherapy may be considered for pain palliation under a case-by-case basis (*e.g.*, treatment of known symptomatic bony metastases). Prior to pursuing radiotherapy, the treating physician should review with the study chair: 1) the reason for radiotherapy, 2) the tumor status (whether progressive disease criteria has been met) and 3) whether resumption of protocol therapy will be considered after completion of radiotherapy. Administration of protocol treatment must be suspended during radiotherapy treatment.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity.

Initiation or increased dose of granulocyte colony-stimulating factors (*e.g.*, granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

Patients are not allowed to receive immunostimulatory agents, including, but not limited to, IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving 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 anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

5.2.3 Excluded Therapies for Participants Receiving 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.

Patient Drug Information Handout and Wallet Card (Appendix B) should be provided to all patients.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression by RECIST version 1.1 criteria,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as defined in section 6.1.1, or at the discretion of the treating physician,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF). Otherwise, treatment may be continued as long as patients are experiencing clinical benefit as assessed by an investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

5.4 Duration of Follow Up

Patients who receive any protocol therapy will be followed for 90 days after removal from protocol therapy or until death, whichever occurs first. Patients removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Atezolizumab

6.1.1 General AE Management and Dose Modification Guidelines

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

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤ 10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the study PI in consultation with CTEP.
The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the 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 irAEs.

6.1.2 Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure . See the Agent Administration Guidelines in this document, including the "Administration of First and Subsequent Atezolizumab Infusions" table for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in

patients receiving atezolizumab in combination with chemotherapy.

Pleural and pericardial effusion

Patients experiencing dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with pre-existing pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions, atezolizumab should be held, and appropriate workup includes cytology, lactate dehydrogenase (LDH), glucose, cholesterol, protein concentrations (with pleural effusions), and cell count.

Pulmonary events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. ● For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab. ● Bronchoscopy or BAL is recommended. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

Event	Management
	• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator and the Medical Monitor.

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

Hepatic Events

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in the table below.

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

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	All events: • Monitor LFTs more frequently until return to baseline values. Events of >5 days' duration: • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.

Event	Management
	• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

Gastrointestinal Events

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in the table below.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b]

	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in the table below.

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including headache, fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests [*e.g.*, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone (ACTH) levels, and ACTH stimulation test] and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone.

Event	Management
	• Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥0.1 mU/L and <0.5 mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks. TSH <0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab.
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Consider referral to endocrinologist, particularly if patient is deemed to have atezolizumab-induced diabetes; if so, obtain C-peptide level paired with glucose, autoantibody levels (e.g. GAD65, islet cell autoantibodies), and hemoglobin A1C level. • If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc.*) reported.

Event	Management
	• Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in the table below.

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended.

Event	Management
	• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

Immune-mediated Cardiac Events

Immune-mediated myocarditis and pericarditis have been associated with the administration of atezolizumab. Management guidelines for cardiac events are provided in the table below.

Immune-mediated Myocarditis

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (*e.g.*, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, *e.g.*, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Immune-mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Event	Management
Immune-mediated myocarditis, Grade 2–4 Immune-mediated pericardial disorders, Grade 2–4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device	

Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab.

However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (*e.g.*, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee *et al*., 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz *et al*., 2017; Adashek and Feldman 2019) including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in the table below.

Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	● Immediately interrupt infusion. ● Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. ● In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ● For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring	● Immediately interrupt atezolizumab infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose.

vasopressors and/or Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Principal Investigator.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors	• Permanently discontinue atezolizumab. • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.

(excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (*e.g.*, CPAP, BiPAP, intubation and mechanical ventilation)	• Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator. • Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz *et al*. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Refer to Riegler *et al*. for information on experimental treatments for CRS.

Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in the table below.

Event	Management
Amylase and/or lipase elevation, Grade 2	Amylase and/or lipase >1.5–2.0 × ULN: • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (*e.g.*, >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN: • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

Event	Management

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

Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of 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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in the table below.

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (*e.g.*, antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above.

Event	Management
	• If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

Neurologic disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders, and specific guidelines for myelitis, are provided in the table below.

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  ○ If event resolves to Grade 1 or better, resume atezolizumab. [b]
	  ○ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
	• For facial paresis:
	  ○ If event resolves fully, resume atezolizumab. [b]
	  ○ If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

Event	Management

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

Immune-mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in table below.

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases.

Event	Management
	• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

Hemophagocytic Lymphohistiocytosis and Marcrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)

  - Platelet count < 100 × 10^9/L (100,000/μL)
  - ANC < 1.0 × 10^9/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181 × 10^9/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in below.

Event	Management
Suspected HLH or MAS	● Permanently discontinue atezolizumab and contact Medical Monitor. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids and/or an immunosuppressive agent. ● 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.

HLH= hemophagocytic lymphohistiocytosis; MAS= macrophage activation syndrome.

6.2 Cobimetinib

Cobimetinib may be dose reduced in this study for drug-related toxicity. Management of certain AEs of particular concern for patients on cobimetinib plus atezolizumab are presented in 6.3. For other AEs, refer to general recommended dose modifications for cobimetinib (presented below, 6.2.1) and atezolizumab (6.1.1). Patients may temporarily

suspend cobimetinib treatment for up to 84 days (12 weeks) if study drug-related toxicity requiring dose suspension is experienced. If cobimetinib is held because of AEs for >84 days, the patient will be discontinued from cobimetinib therapy.

Patients experiencing adverse events attributable to cobimetinib therapy may continue atezolizumab therapy while cobimetinib is held. Patients discontinued from cobimetinib therapy may continue atezolizumab therapy, and will be followed for safety and efficacy as specified in this protocol.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the study PI in consultation with CTEP.

6.2.1 Recommended Cobimetinib Dose Modifications

In order to standardize the management of AEs, suggested treatment management algorithms for adverse events of particular concern for cobimetinib plus atezolizumab are included in section 6.2.0. The following general dose modifications table for cobimetinib is for AEs not specified in the subsequent tables.

Grade (CTCAE v 5.0)[a]	Recommended Cobimetinib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at a 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

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; QD = once daily.
[a] The intensity of clinical adverse events graded by NCI CTCAE v5.0.

Below is a table for cobimetinib dosing upon dose modification:

Dose level	Dose
0	60 mg QD 21 days out of 28 days
(-1)	40 mg QD, 21 days out of 28 days
(-2)	20 mg QD, 21 days out of 28 days

6.2.2 Management of Cobimetinib plus Atezolizumab−Associated Adverse Events of Particular Concern

In general, patients discontinued from combination therapy due to intolerance or adverse

events that are attributable to only one of the two drug therapies may continue monotherapy with the therapy that is not causing the adverse event. For example, a patient removed from cobimetinib therapy after developing retinal vein occlusion may continue atezolizumab monotherapy. Below, recommended management of specific adverse events of particular concern with combination therapy are provided.

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.

Diarrhea or colitis	Management
Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g.*, increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
Grade 1	Continue atezolizumab and cobimetinib. Initiate symptomatic treatment. Suggested regimen: Loperamide: Initiate dose with 4 mg, then 4 mg/6 hr around the clock, alternating with Lomotil. Lomotil (diphenoxylate and atropine): 2 tablets (diphenoxylate 5 mg) every 6 hr around the clock. Continue Lomotil and loperamide until no loose stools for 24 hours. Endoscopy is recommended if symptoms persist for >7 days.

	Monitor closely.
Grade 2	Hold atezolizumab and cobimetinib. Initiate symptomatic treatment. Suggested regimen: Loperamide: Initiate dose with 4 mg, then 4 mg/6 hr around the clock, alternating with Lomotil. Lomotil (diphenoxylate and atropine): 2 tablets (diphenoxylate 5 mg) every 6 hr around the clock. Continue Lomotil and loperamide until no loose stools for 24 hours. If Grade ≤ 2 diarrhea persists after 48 hr total treatment with Lomotil and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). Patient referral to GI specialist is recommended. For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab and cobimetinib according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event.
Grade 3	Hold atezolizumab and cobimetinib. Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with 1–2 mg/kg/day intravenous 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, taper corticosteroids and restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction once at baseline stool

	frequency. Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab and cobimetinib may be considered, after consultation with the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event.
Grade 4	Permanently discontinue atezolizumab and cobimetinib. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist for evaluation and confirmation biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. Consider TNF antagonists for refractory diarrhea.

GI = gastrointestinal; IV = intravenous; LLN = lower limit of normal; NSAID = nonsteroidal anti-inflammatory drug; TNF = tumor necrosis factor.

Amylase and/or lipase increased	Management
Grade 1	Continue atezolizumab and cobimetinib. Monitor amylase and lipase prior to dosing.
Grade 2	Continue atezolizumab and cobimetinib. Monitor amylase and lipase weekly. For prolonged elevation (*e.g.*, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.

Grade 3 or 4	Hold atezolizumab and cobimetinib. Refer patient to gastrointestinal (GI) specialist. Monitor amylase and lipase every other day. If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab.

HEPATOTOXICITY
Hepatotoxicity 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.

Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting	Risk of immune-mediated hepatitis. LFTs should be performed immediately, and LFTs should be reviewed before administration of the next dose of study drug. For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should also include pancreatitis, as described below.
Grade 1 hepatic event	Continue atezolizumab and cobimetinib. Monitor LFTs until values resolve to within normal limits.
Grade 2 hepatic event, ≤5 days	Continue atezolizumab and cobimetinib. Monitor LFTs more frequently until values resolve to baseline values.
Grade 2 hepatic event, >5 days	Hold atezolizumab and cobimetinib. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab and cobimetinib at 1 dose reduction. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. Resumption of cobimetinib may be considered after discussion with the sponsor provided there is evidence of clinical benefit and continued therapy is of interest.
Grade 3 or 4 hepatic event	Permanently discontinue atezolizumab and hold cobimetinib. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

	If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. Resumption of cobimetinib may be considered after discussion with the sponsor provided there is evidence of clinical benefit and continued therapy is of interest.

IV = intravenous; LFT = liver function test; q4w = every 4 weeks; TNF = tumor necrosis factor; ULN = upper limit of normal.

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/Rash	Management
Grade 1	Continue atezolizumab and cobimetinib Initiate symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines). For acneiform rash, consider topical corticosteroids (hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) BID for at least 4 weeks.
Grade 2	Continue atezolizumab and cobimetinib. Consider consultation with a dermatologist. Administer topical steroids. Consider higher potency topical steroids if rash does not improve. For acneiform rash, topical corticosteroids (hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) BID for at least the first 6 weeks. For photosensitivity (intolerable grade 2), withhold cobimetinib for up to 4 weeks. If improved to grade 0 or 1, resume at next lower dose level. If not improved within 4 weeks, permanently discontinue.
Grade 3	Hold atezolizumab and cobimetinib. Consult dermatologist.

	Administer oral prednisone 10 mg or equivalent if the rash is at least possibly attributable to the atezolizumab therapy. If the event does not improve within 48-72 hours, increase dose to 1–2 mg/kg/day or equivalent. Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction if rash resolves to ≤ tolerable grade 2, and systemic dose is < 10 mg oral prednisone equivalent per day. For acneiform rash, consider continuation of topical corticosteroids 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib. For photosensitivity, withhold cobimetinib for up to 4 weeks. If improved to grade 0 or 1, resume at next lower dose level. If not improved within 4 weeks, permanently discontinue.
Grade 4	For photosensitivity (intolerable grade 2), withhold cobimetinib for up to 4 weeks. If improved to grade 0 or 1, resume at next lower dose level. If not improved within 4 weeks, permanently discontinue. For other dermatologic toxicities, permanently discontinue atezolizumab and cobimetinib. Patient may not resume treatment, regardless of benefit. Manage as above.
Persistent and/or severe rash or pruritus, any grade	A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated.
Stevens Johnson syndrome or toxi epidermal necrolysis (any grade)	Additional guidance for Stevens Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

BID = twice daily; BSA = body surface area; PRN = as needed.

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. Chest CT should be reviewed for pulmonary toxicities as well as for disease status.

All pulmonary events	Evaluate thoroughly for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension.
Grade 1	Continue atezolizumab and cobimetinib and monitor closely. Consider serial imaging (repeat imaging scan or x-ray 1-2 weeks later). Consider patient referral to a pulmonary specialist. For recurrent pneumonitis, treat as a grade 3 or 4 event.
Grade 2	Hold atezolizumab and cobimetinib. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage (BAL). Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab at fixed dose and cobimetinib at 1 dose reduction if GGO/infiltrates improving. Permanently discontinue atezolizumab and cobimetinib if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, treat as a Grade 3 or 4 event.

Grade 3 or 4	Hold atezolizumab and cobimetinib. Bronchoscopy or BAL is recommended. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment after consultation with the trial PI. For grade 4, patient cannot resume treatment, regardless of benefit.

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 has been associated with cobimetinib.

Eye Toxicities	Management
Symptomatic eye toxicity (autoimmune uveitis, iritis or episcleritis)	Hold atezolizumab and cobimetinib. Consult ophthalmologist and start topical corticosteroid eye drops. Consider starting prednisone 60 mg/day or equivalent. Taper steroids over ≥ 1 month once symptoms improve to Grade 0/1 (asymptomatic). Atezolizumab may be restarted following resolution of the events with careful monitoring for recurrence. Permanently discontinue atezolizumab for immune−mediated ocular disease that is unresponsive to immunosuppressive

	therapy.
Retinal vein occlusion Any grade	If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. Atezolizumab therapy may be continued.
Serous retinopathy Severity grade assessment based on NCI CTCAE v 5.0 "Eye Disorders – Other" scale. Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Continue atezolizumab and cobimetinib without dose change. Continue ophthalmology follow-up as clinically indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL. Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL.	Hold atezolizumab and cobimetinib. 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. If Grade 2 or 3 serous retinopathy, atezolizumab and cobimetinib dosing should be held until symptoms improve to Grade 1. Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction. If no recovery within 4 weeks, cobimetinib should be permanently discontinued. If Grade 2 or 3 serous retinopathy recurs despite 2 dose level reductions, cobimetinib should be permanently discontinued.
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue atezolizumab and cobimetinib.

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; RVO = retinal vein occlusion; OCT = optical coherence tomography.

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

Decreased LVEF has been seen with cobimetinib. Permanent discontinuation of cobimetinib treatment should be considered if cardiac symptoms are attributed to cobimetinib and do not improve after temporary interruption.

Asymptomatic, absolute decrease in LVEF from baseline of greater than 10% and less than institutional lower limit of normal (LLN)	Withhold cobimetinib for up to 4 weeks; repeat LVEF Resume at next lower dose if all of the following are present • LVEF is at or above LLN, and • Absolute decrease from baseline LVEF is 10% or less Permanently discontinue is any of the following are present • LVEF is less than LLN, or • Absolute decrease from baseline LVEF is more than 10%
Symptomatic LVEF decrease from baseline	Withhold cobimetinib for up to 4 weeks; repeat LVEF Resume at next lower dose if all of the following are present • Symptoms resolve, and • LVEF is at or above LLN, and • Absolute decrease from baseline LVEF is 10% or less Permanently discontinue if any of the following are present • Symptoms persist, or • LVEF is less than LLN, or • Absolute decrease from baseline LVEF is more than 10%

LVEF = left ventricular ejection fraction; LLN = lower limit of normal

Decreased LVEF may also result from immune related cardiomyopathy, a potential risk of atezolizumab therapy. For this reason, atezolizumab should also be held in the setting of decreased LVEF, pending the results of a cardiac workup. This work up should generally include troponin, CPK, cardiac MRI, EKG, and cardiology consultation. Atezolizumab may be restarted on a case-by-case basis as long as LVEF is > 40% (or ≤ 10% absolute decrease from BL) and myocarditis has been excluded. For patients with more severe reductions in the LVEF, atezolizumab may be restarted only if the patient is clinically stable, and after consultation with the trial PI.

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE ELEVATED CPK

Elevated CPK has been reported with cobimetinib. Recommended Dose Modifications for Cobimetinib in Patients with CPK Elevations are presented below.

Description	Management

CPK elevations	Rule out cardiac cause (check EKG, 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). Consider permanent discontinuation of atezolizumab and cobimetinib if there is evidence of clinically significant cardiac injury or rhabdomyolysis. Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
For Grade 3 CPK elevations that are asymptomatic and deemed not clinically significant	Hold atezolizumab and cobimetinib pending workup to rule out immune related cardiomyopathy, myocarditis or other cardiac conditions. Workup should generally include EKG, serum cardiac troponin, and CPK-isoforms M and B fraction. Atezolizumab and cobimetinib may be restarted at previous dose and schedule only if cardiac etiology is ruled out. Recheck CPK at least once a week. If CPK remains Grade 3 or decreases, continue cobimetinib at current dose and schedule.
For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant	Hold atezolizumab and cobimetinib. Rule out immune-related cardiomyopathy, myocarditis or other cardiac conditions. Workup should generally include EKG, serum cardiac troponin, and CPK-isoforms M and B fraction. Recheck CPK within 3 days. When CPK is Grade ≤ 3 and cardiac immune-related cardiomyopathy has been ruled out, atezolizumab and cobimetinib may be resumed with a dose reduction of cobimetinib by 1 dose level on the same schedule (e.g., 60 to 40 mg). If Grade 4 CPK elevation recurs after 1 dose reduction, cobimetinib may be reduced by another dose level (e.g., 40 to 20 mg). Permanently discontinue cobimetinib if Grade 4 CPK elevation recurs after 2 dose reductions of cobimetinib. Atezolizumab may be continued after consultation with the trial PI.

IM = intramuscular.

GUIDELINES FOR MANAGEMENT OF PATIENTS WHO EXPERIENCE HEMORRHAGE
Hemorrhage is a rare side effect that has been reported with cobimetinib. Recommended Dose

Modifications for Cobimetinib in Patients with Hemorrhage are presented below.

Description	Management
Grade 3 events	Interrupt cobimetinib treatment. There is no data on the effectiveness of cobimetinib dose modifications for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. Continue atezolizumab treatment.
Grade 4 events or cerebral hemorrhage (all grades)	Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib.

MANAGEMENT GUIDELINES FOR ENDOCRINE EVENTS

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks. TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.
[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol).

	• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

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

MANAGEMENT GUIDELINES FOR INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors and/or	• Immediately interrupt atezolizumab infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus as needed.

Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	• Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the sponsor-investigator.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the

and mechanical ventilation)	investigator. ● Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

g. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
h. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
i. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
j. Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
k. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
l. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab according to institutional guidelines and the above table. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after considering the benefit-risk ratio.
m. Refer to Riegler et al. [61] for information on experimental treatments for CRS.

MANAGEMENT GUIDELINES FOR NEUROLOGIC DISORDERS

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré	• Permanently discontinue atezolizumab. [c]

syndrome (any grade)	• Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

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

MANAGEMENT GUIDELINES FOR IMMUNE-RELATED MENINGOENCEPHALITIS

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

MANAGEMENT GUIDELINES FOR RENAL EVENTS

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Event	Management
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

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

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

MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED MYOSITIS

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

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

OTHER MANAGEMENT GUIDELINES

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • 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.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

References

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resouce on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) in addition to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agents

7.1.1.1 CAEPR for Atezolizumab

Frequency is provided based on 3097 patients. Below is the CAEPR for Atezolizumab (MPDL3280A).
Version 2.5, November 18, 2024[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia)	
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
		Endocrine disorders - Other (thyroiditis)[2]	
	Hyperthyroidism[2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		*Abdominal pain (Gr 2)*
		Colitis[2]	
	Diarrhea		*Diarrhea (Gr 2)*
	Dysphagia		
	Nausea		*Nausea (Gr 2)*
		Pancreatitis[2]	
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			*Fatigue (Gr 2)*
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis [immune related hepatitis])[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS))[2]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		*Anorexia (Gr 2)*
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Guillain-Barre syndrome[2]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (facial paresis)[2]	
		Nervous system disorders - Other (immune-mediated myelitis)[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		*Cough (Gr 2)*
	Dyspnea		
	Hypoxia		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Nasal congestion		*Nasal congestion (Gr 2)*
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms (DRESS))[2]	
		Skin and subcutaneous tissue disorders - Other (Exanthematous pustulosis)[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	
VASCULAR DISORDERS			
		Vascular disorders - Other (immune-mediated vasculitis)[2]	

*Denotes adverse events that are <3%.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp; Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Cobimetinib

Below is the CAEPR for cobimetinib (RO5514041, GDC0973, NSC 781257). Frequency is provided based on 274 patients.

Version 2.2, March 25, 2020[1]

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		*Anemia (Gr 2)*
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Cardiac disorders - Other (left ventricular dysfunction)	
		Heart failure	
EYE DISORDERS			
	Eye disorders - Other (chorioretinopathy) [2]		
	Eye disorders - Other (eye disorders)[3]		*Eye disorders - Other (eye disorders)[3] (Gr 2)*
		Eye disorders - Other (retinal vein occlusion)[2]	
	Retinal detachment		
GASTROINTESTINAL DISORDERS			

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
Diarrhea			*Diarrhea (Gr 2)*
	Mucositis oral		*Mucositis oral (Gr 2)*
Nausea			*Nausea (Gr 2)*
Vomiting			*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		*Chills (Gr 2)*
Fatigue			*Fatigue (Gr 2)*
	Fever[2]		*Fever[2] (Gr 2)*
Generalized edema[4]			*Generalized edema[4] (Gr 2)*
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		*Alanine aminotransferase increased[2] (Gr 2)*
	Alkaline phosphatase increased[2]		*Alkaline phosphatase increased[2] (Gr 2)*
	Aspartate aminotransferase increased[2]		*Aspartate aminotransferase increased[2] (Gr 2)*
CPK increased			*CPK increased (Gr 2)*
	Ejection fraction decreased		
	GGT increased[2]		*GGT increased[2] (Gr 2)*
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		*Anorexia (Gr 2)*
	Dehydration		*Dehydration (Gr 2)*
	Hyperglycemia		*Hyperglycemia (Gr 2)*
	Hypokalemia		
	Hyponatremia		*Hyponatremia (Gr 2)*
	Hypophosphatemia		*Hypophosphatemia (Gr 2)*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (new primary malignancies, cutaneous and non-cutaneous)[2]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		*Headache (Gr 2)*
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		*Dry skin (Gr 2)*
	Photosensitivity[2]		*Photosensitivity[2] (Gr 2)*
	Pruritus		*Pruritus (Gr 2)*
	Rash acneiform		*Rash acneiform (Gr 2)*
Rash maculo-papular[5]			*Rash maculo-papular[5] (Gr 2)*

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
VASCULAR DISORDERS			
	Vascular disorders - Other (hemorrhage)[6]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Observed in combination with Vemurafenib.

[3]Includes photopsia, blurred vision, vitreous floaters.

[4]Includes peripheral edema, periorbital edema, edema, and facial edema.

[5]Includes rash, dermatitis acneiform, rash pruritic, rash generalized dermatitis, exfoliative rash, rash erythematous, and rash maculo-papular.

[6]Hemorrhage includes cerebral hemorrhage, contusion, ecchymosis, epistaxis, gastrointestinal hemorrhage, hematuria, rectal hemorrhage, retinal hemorrhage, and vaginal hemorrhage.

Adverse events reported on cobimetinib (RO5514041, GDC0973) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that cobimetinib (RO5514041, GDC0973) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (cardiac ventricular thrombosis); Pericardial effusion
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Eye disorders - Other (retinal disorder); Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Dysphagia; Ileus; Lower gastrointestinal hemorrhage; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (autoimmune hepatitis); Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (cholangitis)
INFECTIONS AND INFESTATIONS - Catheter related infection; Gallbladder infection; Infections and infestations - Other (diverticulitis); Lung infection; Paronychia; Sepsis; Skin infection; Thrush; Urinary tract infection
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Electrocardiogram QT corrected interval prolonged; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression); Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Encephalopathy; Facial muscle weakness; Nervous system disorders - Other (immune-mediated encephalitis); Nervous system disorders - Other (intracranial pressure increased); Nervous system disorders - Other (7th nerve palsy); Somnolence; Syncope
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Nasal congestion; Oropharyngeal pain; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Hyperkeratosis
SURGICAL AND MEDICAL PROCEDURES - Surgical and medical procedures - Other (medical device change)
VASCULAR DISORDERS - Hypertension; Thromboembolic event

Note: Cobimetinib (RO5514041, GDC0973) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for the agent that are *bold and italicized* in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Attribution of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 “Disease Progression” in the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Pregnancy loss is defined in CTCAE as “Death in utero.” Any pregnancy loss should be reported expeditiously, as Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, “Death neonatal” under the General disorders and administration SOC.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

7.3.4 Adverse Events of Special Interest

Adverse events of special interest are defined as a potential safety problem, identified as a

result of safety monitoring of the Product. Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). The following AEs are considered of special interest, irrespective of regulatory seriousness criteria:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
  - Treatment- emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Autoimmune hemolytic anemia [atezolizumab]
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis) [atezolizumab]
- Pneumonitis [atezolizumab]
- Pneumonitis [atezolizumab and cobimetinib] Colitis [atezolizumab]
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism and hypophysitis [atezolizumab]
- Systemic lupus erythematosus [atezolizumab]
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis [atezolizumab]
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, and macrophage activating syndrome, hemophagocytic lymphohistiocytosis [atezolizumab]
- Nephritis [atezolizumab]
- Ocular events
  - Retinal vein occlusion [cobimetinib]
  - Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy [cobimetinib]
  - Ocular inflammatory toxicities (e.g., optic neuritis, uveitis, retinitis) [atezolizumab]
- Significant muscular toxicities
  - Rhabdomyolysis or Grade ≥ 3 CPK elevation [cobimetinib and atezolizumab]
  - Myopathies including myositis [atezolizumab]
- Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage [cobimetinib]

- Grade ≥ 3 rash [cobimetinib]
- Grade ≥ 3 diarrhea [cobimetinib]
- Grade ≥ 2 cardiac events including:
  - Symptomatic heart failure or Grade ≥ 2 left ventricular dysfunction [cobimetinib]
- Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis) [atezolizumab]
  - Myocarditis, pericarditis, or atrial fibrillation [atezolizumab]
- Vasculitis [atezolizumab]
- Autoimmune Hemolytic Anemia [atezolizumab]
- Significant liver toxicity [cobimetinib and atezolizumab]
  - Hepatitis, including AST and/or ALT > 10 ×ULN
- Grade ≥ 3 photosensitivity (when administered with vemurafenib) [cobimetinib]

7.4 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions. Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the *Pregnancy Information Form* included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 150 days after the last dose of atezolizumab and 90 days after the last dose of cobimetinib must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

If a female subject becomes pregnant while receiving atezolizumab or within 5 months after the last dose of atezolizumab, a report should be completed and expeditiously submitted to 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 to Genentech as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the atezolizumab should be reported to Genentech, Inc. as an SAE.

Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to

report pregnancy and its outcome to CTEP.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agents

8.1.1 Atezolizumab (NSC 783608)

Other Names: Tecentriq™, MPDL3280A

Classification: monoclonal antibody

M.W.: 150 KD

Mode of Action: anti-PD-L1

Description:
Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte *et al.,* 2007).

How Supplied:
Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Each 20 ml vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

Preparation:
The prescribed dose of atezolizumab should be diluted in 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused with or without a low-protein binding 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), or polyethylene (PE). The prepared solution may be stored at 2°C-8°C for up to 24 hours or at ambient < 25°C (77°F) for 6 hours from the time of preparation. If the dose solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. These times include the storage and administration times for the infusion. Do not shake or freeze infusion bags containing the dose solution.

Storage: 2°C–8°C (36°F–46°F). Vial contents should not be frozen or shaken and should

be protected from direct sunlight.

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

Route of Administration: IV infusion

Method of Administration:
Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with subsequent infusions.

Potential Drug Interactions:
Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

Patient Care Implications:
Male patients and female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 150 days after the last dose of atezolizumab.

Availability
Atezolizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Atezolizumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

Investigator Brochure Availability:
The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an “active” account status and a “current” password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.2 Cobimetinib (NSC #781257)

Chemical Name: (*S*)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl]
[3 hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate

Other Names: COTELLIC®, RO5514041, GDC0973

Classification: MEK inhibitor
Molecular Formula: $C_{46}H_{46}F_6I_2N_6O_8$

M.W.: 1178.69 g/mol as hemifumarate salt
531.31 g/mol as free base

Approximate Solubility: At 37°C, the solubility of cobimetinib is 0.744 mg/mL in water

Mode of Action: Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2.

Description: Cobimetinib API is a hemifumarate salt, appearing as a white to off-white solid.

How Supplied: Genentech supplies and CTEP, DCTD, NCI distributes Cobimetinib as a 20-mg film coated, immediate-release tablets debossed on one side with "COB". Drug concentrations and strengths of tablet drug products are expressed as the free-base equivalents. The tablet formulation consists of the cobimetinib drug product and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate (non-bovine), and Opadry White film coat. All excipients used in the tablet formulation are compendial (USP/NF and/or EP) grade with the exception of the film coating. The tablet coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol 3350, and talc. The ingredients in the film coating are compendial. Each bottle contains 63 tablets.

Storage: Store at room temperature below 30°C (86°F).
If a storage temperature excursion is identified, promptly return cobimetinib to below 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

Route*(s)* of Administration: oral

Method of Administration: cobimetinib can be administered with or without food

Potential Drug Interactions*:*
Avoid concurrent use of cobimetinib and strong or moderate CYP3A inhibitors. If concurrent short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable, consider reducing the dose of cobimetinib while on CYP3A inhibitor. Coadministration of cobimetinib with a strong CYP3A inducer may decrease cobimetinib systemic exposure by more than 80% and reduce its efficacy. Avoid concurrent use of cobimetinib and strong or moderate CYP3A inducers including but not limited to carbamazepine, efavirenz, phenytoin, rifampin, and St. John's Wort.

Cobimetinib is a substrate of efflux transporter P-glycoprotein (P-gp), but is not a substrate of Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptide (OATP1B1 or OATP1B3) or Organic Cation Transporter (OCT1) in vitro. Drugs that inhibit P-gp may increase cobimetinib concentrations. In vitro data suggest that cobimetinib at clinically relevant concentrations does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or OCT2.

Coadministration of a proton pump inhibitor, rabeprazole 20 mg once daily for 5 days, with a single dose of 20 mg COTELLIC under fed and fasted conditions did not result in a clinically important change in cobimetinib exposure.

Reproductive Risks:
Based on its mechanism of action and findings from animal reproduction studies, cobimetinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use adequate contraception during treatment and for a minimum of 2 weeks after the last dose of cobimetinib.

Investigator Brochure Availability:
The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

Investigator Brochure Availability:

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management

Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch/Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.
In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Summary Table for Specimen Collection

Time Point	Specimen and Quantity	Send Specimens to:
Archival		
	• Formalin-fixed, paraffin-embedded (FFPE) tissue block (preferred)[1] If a block is not available, then submit: • 1 H&E stained slide (3-5 µm) • 30-50 unstained, air-dried, uncharged slides (10 µm). If not feasible, then a minimum of 20 unstained air-dried unch slides (10 µm) should be submitted with minimum tumor content of 30-40%[2]. • 1 H&E stained slide (5 µm) • 5 unstained, air-dried, charged slides (5 µm)	EET Biobank
Baseline		
	• 6 tissue cores in formalin[3]	EET Biobank
Cycle 1, Day 1 (C1D1)		
	• 20 mL whole blood in cfDNA Streck tubes • 20 mL whole blood in sodium heparin tubes	EET Biobank
Cycle 1, Week 4 (Day 22-28)		
	• 6 tissue cores in formalin[3]	EET Biobank
Cycle 2 Day 1		
	• 20 mL whole blood in cfDNA Streck tubes • 20 mL whole blood in sodium heparin tubes	EET Biobank
Progression/Relapse		
	• 20 mL whole blood in cfDNA Streck tubes • 20 mL whole blood in sodium heparin tubes • 6 tissue cores in formalin (optional)[3]	EET Biobank

[1] *For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave.* If submitting slides, then slides must be processed in order, and

numbered sequentially (*e.g.*, H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51).
[2] Submission of specimens with <30% tumor content may not provide sufficient material for analysis
[3]For new biopsies, the Tissue Biopsy Verification Form (Appendix D), a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank.

9.2 Specimen Collection and Shipping Kits

Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via Kit Management system (https://kits.bpc-apps.nchri.org). Sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website. Kits are not provided for submitting archival tumor tissue submission. Sites must use institutional supplies.

9.3 Specimen Collection

Biopsies are mandatory and disease amenable to core biopsy is an eligibility requirement. Immunohistochemical studies will be performed on tumor tissue. Additional portions of this material will undergo extraction of nucleic acids for whole exome sequencing and RNA sequencing. Biopsies will be collected at baseline (after registration but prior to cycle 1, day 1 with no systemic treatment between biopsy and cycle 1, day 1) and again during cycle 1, week 4. Biopsies at progression are optional. Biopsy modality will be determined by the treating physician based on location of the lesion and safety of various approaches. If, after the start of treatment, circumstances render the research biopsy unsafe, it should not be attempted. The safety of the biopsy will be determined by the treating physician and the physician performing the biopsy and will consider location, including proximity to vasculature, and organ site.

The first pass will be used for on-site examination of the material, to determine presence and quality of lesional tissue. All remaining tissue will be collected in formalin and shipped overnight to the EET Biobank at Nationwide Children's Hospital. Specimen shipment kits will be provided.

9.3.1 Archival tissue

An archival tumor formalin-fixed paraffin-embedded tissue block taken prior to the patient's initial treatment with a PD-1 or PD-L1 inhibitor should be submitted, when available.

If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide (3-5 µm)

- Thirty to fifty (30 – 50) 10 µm unstained air-dried uncharged slides (preferred). If not feasible, then a minimum of twenty (20) 10 µm unstained air-dried uncharged slides should be submitted with a minimum tumor content of at least 30%. Submission of specimens with <30% tumor content may not provide sufficient material for analysis [include for NGS-based biomarkers, if archival tissue is likely be to be biopsies; uncharged slides at 10-microns (µm) are preferred for slides intended for DNA/RNA extractions.]
- One (1) H&E stained slide (5 µm)
- Five (5) 5 µm unstained, air-dried, charged slides.

Include a de-identified copy of the corresponding pathology report in the package and upload to the Specimen Tracking system in Rave. Pathology report must be labeled with the Universal ID, patient study ID, and include the SPID, block number, procedure date, and diagnosis.

Upon receipt, slides should be vacuum sealed and refrigerated for long-term storage by the biorepository.

9.3.2 Oversight of Tumor Specimen Collection

It is the responsibility of the submitting institution to provide only those biospecimens that are not necessary for diagnostic purposes.

Acceptable Biopsy Procedures and Specimen Types

- Core needle biopsy tissue (6 cores if possible).
- Percutaneous biopsy with local anesthetic.
- Excisional cutaneous biopsy with local anesthetic.
- Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications <2%.
- Biopsy with removal of additional tumor tissue during a medically necessary mediastinoscopy, open surgery, laparoscopy, gastrointestinal endoscopy, peritoneal, bronchoscopy, or craniotomy.
- Removal of additional tumor tissue during a medically necessary surgical procedure.
- Mediastinal, open surgical or laparoscopic, gastrointestinal, peritoneal or bronchial endoscopic biopsies are permitted ONLY when obtained incidentally to a clinically necessary procedure and not for the sole purpose of the clinical trial. No laparoscopic, or endoscopic or open surgical procedure will be performed solely to obtain a biopsy for this protocol.

Contraindications to percutaneous biopsy:

- Significant coagulopathy or anticoagulation treatment that cannot be adequately corrected.
- Severely compromised cardiopulmonary function or hemodynamic instability.
- Lack of a safe pathway to the lesion.
- Inability of the patient to cooperate with, or to be positioned for, the procedure.

If a site is deemed appropriate for biopsy with minimal risk (no more than 2% risk of serious complication requiring hospitalization) to the participant by agreement between the investigators and Interventional Radiology, an attempt at biopsy will be made.

9.3.3 Biopsy Collection Procedure

Six (6) core biopsies at least 1 cm in length will be obtained (if possible) through Interventional Radiology by a percutaneous approach using a 16-18-gauge needle. Only percutaneous biopsies will be performed on patients with solid tumors. However, excisional biopsy is allowed if indicated and can be used for analysis.

Kits are supplied by the EET Biobank for specimens shipped to the Biorepository by the EET Biobank at Nationwide Children's Hospital. Kits should be ordered before specimen collection.

9.3.3.1 Standard Operating Procedure for Collection of Biopsy Specimens:

Pre-label formalin specimen jars according to instructions in section 9.5.1.2. Tumor tissue shipped in formalin will be paraffin-embedded at the EET Biobank.

Specimen size requirement is as follows:
Surface area of 25mm^2 is optimal. Minimum is 5mm^2 and
Volume: 1mm^3 optimal. Minimum volume is 0.2mm^3.

Biopsy Collection Methodology:

1) Ensure that biopsies are only performed by qualified personnel. Follow institutional policies and consenting procedures in collecting biopsies.
2) Ensure that specimen transportation to the pathology laboratory or designated processing laboratory is arranged to allow for quick tissue preservation.
3) Immediately place each core in a tissue cassette and transfer into specimen jars, containing 10% neutral-buffered formalin. Up to 2 cassettes may be placed in each formalin jar.
4) Perform fixation at room temperature (20-25°C). Record the date and time that the tissue was added to formalin and enter it in the Comment field into the Sample Tracking System (Rave) for all submitted specimens. The optimal duration of fixation should be 16-24 hours by the time it is received at the EET Biobank.
5) Ship the specimen to the EET Biobank (FedEx Priority Overnight strongly preferred) for processing the day of collection.

9.3.4 Blood Collection in cfDNA Streck tubes:

1) Label two cfDNA Streck tubes, according to instructions in section 9.5.1.1.
2) Collect 20 mL of blood into the pre-labeled tubes and invert to mix. Note: blood must be thoroughly mixed to ensure preservation of specimen.
3) After collection, blood in cfDNA Streck tubes should never be refrigerated, as this

will compromise the specimen. Blood collected in cfDNA Streck tubes is stable at room temperature.
4) Ship on the day of collection (whenever possible) according to the instructions below.

9.3.5 Blood Collection in NaHep (green-top) tubes:

1) Label NaHep (green-top) tubes according to instructions in section 9.5.1.1.
2) Collect 20 mL of blood into the pre-labeled tubes and gently invert to mix.
3) After collection, blood in NaHep should be refrigerated until shipment.
4) Ship on the day of collection according to the instructions below (including labeling the shipping box with "CIMAC Blood" and the collection date and time).

9.4 Sample Tracking System Instructions

9.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
- Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies without a corresponding pathology report, the radiology and operative report(s) must also be uploaded into Rave, when available. Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.

Additionally, please note that the STS software creates pop-up windows when reports are

generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report must be included with all sample submissions.

9.4.2 Specimen Labeling

Note: CIMAC blood must include collection time because of processing requirements.

9.4.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and time (for CIMAC blood specimens) (to be added by hand)

9.4.2.2 Tissue Specimen Labels

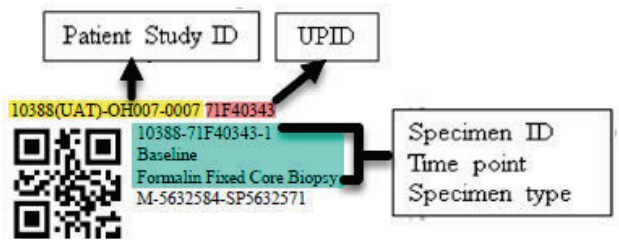
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, formalin-fixed paraffin-embedded [FFPE] Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number (when applicable)
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)
- Slide section number (only if archival tissue is submitted as slides) (to be added by hand)

9.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5” high and 1.28” wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

9.4.3 Overview of Process at Treating Site

9.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

- Site enters registration data into OPEN during one or more steps.
- IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
- IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

9.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the Histology and Disease form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding Prior Therapies. Enter the initial clinical specimen data:

- Specimen Tracking Enrollment CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the Print Labels CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and time (for CIMAC blood samples) on each label.
- After collection, labeled specimens should be shipped promptly, not stored and batched.
- Apply an extra specimen label to *each* report before scanning. Return to the Histology and Disease form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to Specimen Tracking Enrollment CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or the Tissue Biopsy Verification form (Appendix D). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document (either by adding a label or hand writing).

Step 3: Complete specimen data entry.

- Specimen Transmittal Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- Shipping Status CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- Copy Shipping CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the Copy Shipping form to derive common data into additional Shipping Status forms. A few unique fields will still need to be entered in Shipping Status.

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the Shipping Status CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

9.5 Shipping of Specimen(s) to the EET Biobank

9.5.1.1 Schedule of Shipment

- Tumor tissue cores collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection. Tissue can be collected Monday through Wednesday, and shipped overnight (FedEx Priority Overnight is strongly preferred to avoid potential delays, which will negatively impact specimen quality) for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.
- Fresh blood specimens may be collected and shipped Monday through Friday. Saturday delivery is only available for shipments of fresh blood.
- Archival FFPE tissue can be shipped Monday through Thursday

9.5.1.2 Shipping Specimens from Clinical Site to the EET Biobank

The same box sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. The pathology report must state the disease diagnosis made by the reviewing pathologist.

For formalin-fixed biopsies, the surgical and/or radiology report, Tissue Biopsy Verification Form (Appendix D), and the diagnostic anatomic pathology report must be uploaded to the ETCTN specimen tracking system and included in the package, or the specimen will not be processed. When available, upload the anatomic pathology

report corresponding to the biopsy procedure.

9.5.1.2.1. Required Forms for Blood and Tissue Submission

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	Required Forms
Archival	1. Shipping List 2. Corresponding Pathology Report
New Biopsy	1. Shipping List 2. Tissue Biopsy Verification Form (Appendix D) 3. Diagnostic Pathology Report 4. Operative and/or Radiology Report
Whole Blood in Streck cfDNA or sodium heparin tubes	1. Shipping List

9.5.1.3 Shipping Instructions

Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. *Note: If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. Do not refrigerate, freeze, or microwave.*
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. Note: The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach a neon sticker on the outside of the shipping container that says “CIMAC Blood” and write on the blood collection date and time (e.g., 01/01/2019, 1:32 pm) of shipping whole blood in NaHep.
12. Attach an Exempt Human Specimen sticker to the side of the box.

13. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

Packaging Ambient Tissue in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed. The lid of each formalin jar should be wrapped in parafilm. Absorbent material must be placed around each formalin jar.
2. Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
3. Place specimens into the secondary pressure vessel and surround with bubble wrap.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely. Place the lid on the secondary pressure vessel and set it inside the kit chamber.
5. Place a copy of the shipping manifest and corresponding reports such as operative or radiology reports and Tissue Biopsy Verification Form into the insulated shipping container. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container, to prevent specimens from freezing.
6. Place the lid on top of the container. Close the outer flaps and tape shut.
7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

9.5.1.4 Shipping address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897
E-mail: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per sample shipment to the EET Biobank, utilizing the site screening and base intervention payments.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

9.5.1.5 Contact Information for Assistance:
For all queries, please use the contact information below:

EET Biobank
Phone: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

Any other questions regarding biospecimens should be directed to the overall study PI, Dr. Stephen Liu, [redacted] or email [redacted]

9.6 Integral Laboratory or Imaging Studies

Not applicable.

9.7 Integrated Correlative Studies

9.7.1 *Serial TIL Analysis by Multiplex IHC – Integrated Laboratory Correlative Study*

Inhibition of MEK in preclinical models with cobimetinib has led to an increase in T-cell infiltration of the tumor (Ebert *et al*., 2016). One of the hypotheses being tested in this study is that use of cobimetinib will increase the density of CD8+ T-cells in the tumor which will subsequently overcome primary resistance to use of a checkpoint inhibitor. Multiplex IHC has been used to assess the change in the CD8+ T-cell population in patients with melanoma (Tumeh *et al.*, 2014). Among patients receiving treatment with a PD-1 inhibitor, a greater increase in CD8+ cell density corresponded with a decrease in tumor size. We hypothesize that patients receiving the combination of atezolizumab and cobimetinib will have increased CD8+ T cell infiltration in tumors as compared to patients receiving atezolizumab alone. Further, we hypothesize that patients with increased CD8+ T cell infiltration will have a better clinical outcome regardless of treatment group.

Biopsies will be collected prior to therapy and after 1 cycle of therapy to assess changes in CD8+ T-cell infiltration. These studies will either confirm or reject the hypothesis that MEK inhibition increases T-cell infiltration. If an increase in CD8+ T-cell infiltration with MEK inhibition is confirmed and durable responses are achieved, this combination warrants further study, perhaps in earlier lines of therapy. If an increase in CD8+ T-cell infiltration with MEK inhibition is confirmed but durable responses are not seen, CD8+ T-cell infiltration may be necessary but not sufficient and other combinations may be warranted. If no increase in CD8+ T-cell infiltration is seen, further investigation is necessary to explain this discrepancy, which may be disease specific.

In this correlative study, we will use multiplex IHC to assess CD8+ T-cell density over the course of therapy. Biopsies taken immediately prior to enrollment will be compared to biopsies taken at the end of cycle 1. We expect an increase in CD8+ T-cell density with therapy, particularly in patients who respond to therapy. This will be considered an integrated biomarker for the clinical study.

These analyses are critical to understanding the effect of MEK inhibition of T-cell infiltration and demonstrating the proof of principal *in vivo*, and are felt to justify the risk of biopsy.

While the primary focus is on CD8+ lymphocyte density, additional markers will be included in the panel including CD3, FOXP3, CD20, CD66b, PD-1, PD-L1, DC-LAMP, and HLA-DR. The method used can accommodate 8 markers routinely but if tissue integrity is good, additional markers can be added a clear priority, acknowledging that some markers need to be placed earlier in order of staining to avoid loss of sensitivity.

9.7.1.1 Specimen(s) and Processing at the EET Biobank

Formalin-fixed tissue at Baseline (or Archival if Baseline tumor biopsy is not available), C1W4, and Progression time points will be used for this assay. Tumor tissue will be processed and embedded upon receipt at the EET Biobank. FFPE blocks will be stored at room temperature until distribution for testing. Unstained slides should be vacuum sealed upon receipt and refrigerated for long-term storage by the biorepository.

When CIMAC is ready to perform the mIHC, a sample request letter will be sent to the Biobank to request the slides to be cut for the assay.

9.7.1.2 Site Performing Correlative Study

This integrated correlative study will be performed through the CIMAC network.

9.8 Exploratory/Ancillary Correlative Studies

9.8.1 *Whole Exome Sequencing of Tumor Specimens and Gene Expression Analysis by RNA Sequencing for Confirmation of Expression of Neoantigens and Characterization of the Tumor Microenvironment – Exploratory/Ancillary Laboratory Correlative Study*

While immunotherapy holds great promise for durable treatment benefit, the benefit is limited to a subset of patients and we lack reliable means to identify this subset. Expression of PD-L1 by IHC is currently used in this manner but its positive predictive value is too low, its negative predictive value too high. There is a relationship between the genomic signature in NSCLC and response to immunotherapy. In analyses of patients with NSCLC treated with pembrolizumab, higher somatic nonsynonymous mutation burden (above the median) was associated with a higher response rate (63% vs. 0%) and longer PFS (HR 0.19, 95% CI 0.05-0.70). It is not clear, however, whether all somatic mutations carry equal value, as specific mutations may be relevant. Specific defects in the interferon-receptor signaling pathway such as mutations in Janus kinase 1 or 2 (JAK1, JAK2) have been associated with acquired resistance to PD-1 inhibitors (Zaretsky et al., 2016). It is also not clear how tumor mutation burden varies over time.

Here, we propose whole exome sequencing of tumor specimens to further explore a relationship between mutational profile and outcomes. Similar analysis will be done on

archival specimens obtained prior to the initial PD-1 or PD-L1 therapy, on biopsy tissue following this initial PD-1 or PD-L1 therapy but prior to protocol treatment (Baseline), and on progression tissue to assess changes in mutational burden during various types of treatment.

DNA will be isolated from blood collected at baseline to be used as a germline control for whole exome sequencing (if a baseline timepoint is not available for a patient, a non-baseline timepoint can be used for germline instead).

Whole Exosome Sequencing (WES) DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System at the Molecular Characterization Laboratory (MoCha), Frederick National Laboratory for Cancer Research. WES will be performed at an average sequence depth of ≥200X for tumor samples and ≥80X for matched normal PBMC samples. In this assay, 250ng of genomic DNA is fragmented and the resulting library is enriched using a hybridization bait set specific for the coding regions of the genome.

The captured DNA libraries are sequenced on the Illumina NovaSeq 6000 or NovaSeq X and the resulting sequenced DNA is aligned to the reference genome to identify variant alleles.

Comprehensive bioinformatics approaches will be utilized to identify somatic mutations:

- The fastq files are mapped to human genome reference hg19 using BWA. Picard based tools and inhouse scripts are used to assess mapping quality, mean coverage of the samples.
- Single nucleotide variants (SNV) and short insertions and deletions (indels) will be identified using GATK 3.4 (Mutect) and Strelka (v1.0.14).
- Variants will be annotated using ANNOVAR
- Copy number variants will be identified using Sequenza (v2.1.2) and other related tools
- HLA genotype will be inferred using PolySolver.
- Somatic neoantigens will be predicted using NetMHCpan-3.0, and expression of neoantigens will be assessed from tumor RNA-Seq data (see below).

RNA libraries will be generated using the Illumina's RNA Access Library Kit at MoCha, a hybridization-based strategy to enrich for coding RNAs from total RNA libraries. In this assay, cDNA synthesis is primed from total RNA using random primers and converted into a library. The library is then enriched for coding RNA by positive selection using a pool of oligos specific to coding exons of the genome. This method effectively depletes both non-coding RNA and ribosomal RNA, to allow analysis of the mRNA fraction of the transcriptome in FFPE tissue samples.

A number of bioinformatics approaches will be used to analyze the RNA-Seq data

- Transcript read counts and RPKM values will be determined using standard tools, and possibly alignment-free tools such as Salmon.

- Clustering algorithms (including NMF clustering) will be used to identify gene modules of interest
- Tools including TIMER and Cibersort will be employed to assess immune cell subtypes in tumor samples

Finally, gene expression analysis has been utilized to contextually evaluate immune biomarkers and identify signatures associated with immune escape and response to therapy. In NSCLC, atezolizumab improved overall survival in patients with tumors characterized by high expression of T-effector-associated and interferon-y-associated genes (HR 0.45; 95% CI 0.24-0.77)(*17*).

RNA sequencing will be performed on archival specimens obtained prior to initial PD-1 or PD-L1 therapy, on biopsy tissue obtained following initial PD-1 or PD-L1 therapy but prior to protocol treatment (Baseline), on biopsy tissue obtained following protocol treatment (C1W4), and at progression. We aim to study changes and dynamics in the immune cell subsets over time and investigate them in the context of clinical outcome.

9.8.1.1 Specimen(s) and Processing at the EET Biobank

Archival FFPE if available, and formalin-fixed tissue at Baseline, C1W4, and Progression time points will be used for sequencing assays for WES and RNAseq as noted in Section 9.8.1.

Tissue in formalin will be processed and embedded upon receipt at the EET Biobank. When the assay labs are ready to perform sequencing, sections will be cut from the biopsies for nucleic acid extraction (Biomarker Table in Section 9.9 shows the analysis timepoints for each assay). For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction.

DNA will be banked in a stock vial and RNA will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing. Nucleic acid from archival FFPE will be used for WES/RNAseq (MoCha) while all other specimens will be apportioned between MoCha and (for TCRseq, if specimen remains) CIMAC/Adaptive.

DNA will be extracted from blood collected in cfDNA Streck tubes at the Cycle 1 Day 1 time point following plasma processing. DNA will be stored in a -80°C freezer until distribution for future testing.

9.8.1.2 Site Performing Correlative Study

This correlative study will be funded and performed by the Molecular Characterization Laboratory (MoCha), Frederick National Laboratory for Cancer Research.

9.8.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha, Frederick National Laboratory for Cancer Research (FNLCR)
Attn: [redacted]
1050 Boyles St.
Bldg. 459, Rm. PPD
Frederick, MD 21702

9.8.1.4 Contact Information for Notification of Specimen Shipment

[redacted] mochasamplereceiving@nih.gov

9.8.2 *PD-L1 expression – Exploratory Laboratory Correlative Study*

PD-L1 expression is a predictive biomarker for response to PD(L)1 antibody therapy, though it is neither perfectly sensitive nor specific for response. Responses will be reported based on PD-L1 expression (by 22C3 PD-L1 assay) as either negative, positive, low, or high. In addition, changes in PD-L1 expression between archival specimens (prior to initial immunotherapy) and pre-study baseline specimens (after initial immunotherapy) and on-study specimens (after study treatment) will be noted and reported.

9.8.2.1 Specimen(s) and Processing at the EET Biobank

Archival FFPE if available and formalin-fixed tissue at baseline time points will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank. When CIMAC is ready to perform PD-L1 analysis, a sample request letter will be sent to the Biobank to request the slides to be cut for the assay.

9.8.2.2 Site Performing Correlative Study

This correlative study will be performed through the CIMAC network.

9.8.3 *CyTOF – Exploratory/Ancillary Laboratory Correlative Study*

In addition to tissue-based approaches, the effect of the combination treatment on peripheral immunity should be addressed, as it may eventually be easier to define circulating biomarkers, as well as to elucidate mechanisms of action at play. Characterizing changes in the composition and functionality of peripheral blood can be done using mass cytometry CYTOF, which allows up to 40 markers to be combined at a single cell level for detailed analysis of phenotype and immunomodulatory molecule expression. We and others have applied CYTOF analysis in the context of early NSCLC lesions, to compare them to adjacent non-involved tissue, and found dramatic changes in T cell (including Tregs), NK cell, and myeloid cell nature and frequency (*9, 10*). We propose to use these methods for detecting changes in lymphoid and myeloid cell modulation in peripheral blood throughout treatment, as a surrogate for immune responses and potential for correlation with clinical outcome. In particular, PD-1 expression on T cells has been demonstrated in NSCLC as a potential biomarker of importance after PD-1 targeting agents (*11, 12*).

High-dimensional single cell monitoring is a key strategy to elucidate complex phenotypic and functional characteristics of heterogeneous immune populations. This is a broadly applicable approach that can provide valuable insights into disease mechanisms and therapeutic responses and potentially identify correlative cellular biomarkers in the context of many different trials. Some of the key challenges in maximizing the impact of cellular immune monitoring are to increase the number of parameters that can be examined simultaneously in a single sample while minimizing experimental and technical variability. The MS-CIMAC has established a robust cytometric platform addressing both of these challenges using a CyTOF2 mass cytometer.

Mass cytometry (*31*) uses antibodies conjugated to rare-earth metals, resulting in cleaner, higher-dimensional data compared to conventional flow cytometry. With it, we can evaluate up to 55 independent parameters in a single sample, including over 40 antibodies against surface and intracellular targets, or nucleic acid labels to identify cells, assess their viability and evaluate cell cycle. We can also use barcoding reagents to enable pooled samples analysis to minimize experimental variability, improve sample throughput and reduce costs. Because of its sample-sparing nature, we propose to use CyTOF for phenotypic and functional analyses of PBMC as well as single cell suspensions of fresh tumors whenever available, with one million viable cells providing ample information.

The MS-CIMAC has invested heavily to establish a comprehensive CyTOF mass cytometry pipeline. It includes optimized sample processing SOPs, a reagent bank of over 500 metal-conjugated antibodies, a range of curated immune profiling panels, custom antibody conjugation services, and an efficient data processing pipeline. As one of the most active clinically-focused mass cytometry programs in the country (*10, 16, 28, 32-50*), we routinely apply high dimensional mass cytometry in a range of applications, including phenotypic characterization of rare clinical samples, functional studies of multiplexed intracellular cytokine detection and phosphoprotein detection.

A consensus panel inspired by HIPC efforts and agreed upon among CIMACs will be used to quantify changes in all major subsets from peripheral blood, as well as to assign them functional orientations. We will assess differential effects of treatment arms on CD8, CD4 T cells, regulatory T cells, B cells, NK cells, and myeloid cell subsets including dendritic cells, basophils, and neutrophils potentially remaining after blood processing and cryopreservation. These will be analyzed using clustering algorithms in a pipeline developed at Mount Sinai, along with the help of tools such as Cytobank and Astrolabe. Beside frequency differences across time points and between cohorts, changes in functional markers (memory, activation, chemokine receptors related to Th1/Th2/Th17, costimulatory markers such as ICOS and coinhibitory markers such as LAG3, TIM3…) will be assessed as well.

9.8.3.1 Specimen(s) and Processing at the EET Biobank

Blood collected in NaHep (green top) tubes at Cycle 1 Day 1(before protocol treatment),

on day 1 of cycle 2 and at or after the time of progression (end of treatment visit) will be used for this study.

Upon receiving the sodium heparin green-top tubes from the collection site, the EET Biobank will pool all samples from a blood draw at one timepoint and prepare plasma and PBMCs following a Ficoll-Paque protocol as outlined in the CIMAC umbrella protocol. Plasma is stored in a -80°C freezer and PBMCs are stored in a liquid nitrogen vapor phase freezer until distribution.

At the end of the study, upon request by CIMAC/NCI the PBMCs will be retrieved from storage and sent for testing.

9.8.3.2 Site Performing Correlative Study

This correlative study will be performed through the CIMAC at the Icahn School of Medicine at Mount Sinai.

9.8.4 *Olink – Exploratory/Ancillary Laboratory Correlative Study*

Plasma analytes may provide important insight into local mechanisms that are also detectable in circulation. We propose to measure 92 immuno-oncology related analytes from the Olink platform, that includes cytokines, chemokines, but also PD-L1 and PD-1 which may be shed as exosomes in plasma, and to assess their changes from pre- to post-treatment. Rationale for measuring soluble PD-L1 was described in early NSCLC (*12*).

Measuring soluble analytes is an attractive way to relate changes to treatment and potentially to local tumor events, because secreted proteins or molecules shed through exosomes can be repeatedly sampled in the periphery. The Proseek Olink Proteomics platform operating on a Fluidigm Biomark HD microfluidic PCR is a simple yet quantitative and reproducible assay to measure levels of molecules related to inflammation and cancer in peripheral serum or plasma. Mount Sinai-CIMAC is the first center in the US that has been trained and certified to perform these assays in house. The Proximity Extension Assay (PEA) technology that underlies these assays relies on dual antibody recognition and incorporates several innovative QC steps to evaluate each step of the assay protocol, resulting in an extremely robust assay. Critically, we will use Olink's Immuno-Oncology panel of 92 analytes curated for their potential functional role in cancer immunotherapy: in addition to profiling an array of cytokines, chemokines and growth factors, this platform also allows detection of circulating immune co-stimulatory and inhibitory molecules, relevant in the current proposed trial.

9.8.4.1 Specimen(s) and Processing at the EET Biobank

Blood collected in NaHep (green top) tubes at Cycle 1 Day 1 (before protocol treatment), on day 1 of cycle 2 and at or after the time of progression (end of treatment visit) will be used for this study.

Upon receiving the sodium heparin green-top tubes from the collection site, the EET Biobank will pool all samples from a blood draw at one timepoint and prepare plasma and PBMCs following a Ficoll-Paque protocol as outlined in the CIMAC umbrella protocol. Plasma is stored in a -80°C freezer and PBMCs are stored in a liquid nitrogen vapor phase freezer until distribution.

At the end of the study, upon request by CIMAC/NCI, the plasma will be retrieved from storage and sent for testing.

9.8.4.2 Site Performing Correlative Study

This correlative study will be performed through the CIMAC network.

9.8.5 *ELISA (Grand Serology) – Exploratory/Ancillary Laboratory Correlative Study*

In complement to soluble analytes, we will also query changes in circulating plasma antibody to known tumor antigens found frequently in advanced NSCLC (NY-ESO-1, MAGE-A, XAGE, TP53…) using a high-throughput ELISA platform named Grand Serology (*6*). The rationale for these is to characterize antigen-specific changes in tumor immunity that may be induced by combination treatment, and have potential predictive value in NSCLC (*13*). We have described presence of frequent tumor-antigen specific antibodies both in the periphery and at the tumor site (*6*). Moreover, antibodies to p53 or cancer-testis antigens should reflect tumor antigen expression, which is also known to be prognostic value in NSCLC (*14-16*). The Grand Serology assay is therefore important because it may assign specificity to peripheral immune responses that could highlight differential immunogenicity and eventual correlation with clinical variables.

One approach to test whether tumors become more immunogenic as a result of immunotherapy is to measure naturally occurring antibodies to tumor antigens in patient serum or plasma. Autologous serotyping has resulted in a growing list of immunogenic human cancer antigens (*51*), including mutational, overexpressed, oncogenic viral, differentiation, and cancer-testis antigens. These antigens, though usually intracellular, reflect the immune system's capacity to detect abnormalities associated with neoplasia. The presence of antibodies to tumor antigens can be used as a marker of tumor presence or progression, but may also help generate T cell responses via immune complexes with cognate antigen. In some cases, such as the cancer/testis antigen NY-ESO-1, serum antibodies are associated with spontaneous T cell responses in peripheral blood. We propose to test the hypotheses that immunotherapy leads to induction or increase in immunity to locally expressed antigens by assessing serological changes pre-post treatment*, and that the serological repertoire in patients may be useful as a prognostic or predictive tool.*

We have shown that presence of baseline serum antibodies to NY-ESO-1 was correlated with clinical benefit to ipilimumab in metastatic melanoma patients (*52*), and that changes in NY-ESO-1 antibody titers also correlated with clinical events in a patient with abscopal response (*53*). More generally, using serological markers as a surrogate for

presence of antitumor immunity is proposed as a quick and affordable way to assess tumor immunocompetence and response.

We will perform an assay that we named Grand Serology: A series of known tumor antigens will be assessed in a hypothesis-driven manner for their capacity to elicit autoantibodies in treated patients. Using ELISA as previously described(*54*), we routinely test a series of 25 tumor antigens, including mutational, stem-cell, and cancer-testis antigens such as TP53, NY-ESO-1, SOX2, PRAME, WT1, MAGE-A3, SSX2, etc., most of which already have demonstrated immunogenicity in various solid and some hematologic tumors. Grand Serology is also ideally suited to test for potential for antigen spreading, i.e., development of seroreactivity to antigens unrelated to immunogens, which is a useful measurement to assess in immunotherapy. *We propose to use this assay systemically as a unifying measurement throughout all NCI-supported immunotherapy trials, to define baseline immunogenicity, quantify changes or induction in peripheral immunity with local or systemic treatments, and probe potential prognostic value.*

9.8.5.1 Specimen(s) and Processing at the EET Biobank

Blood collected in NaHep (green top) tubes at Cycle 1 Day 1 (before protocol treatment), on day 1 of cycle 2 and at or after the time of progression (end of treatment visit) will be used for this study.

Upon receiving the sodium heparin green-top tubes from the collection site, the EET Biobank will pool all samples from a blood draw at one timepoint and prepare plasma and PBMCs following a Ficoll-Paque protocol as outlined in the CIMAC umbrella protocol. Plasma is stored in a -80°C freezer and PBMCs are stored in a liquid nitrogen vapor phase freezer until distribution.

At the end of the study, upon request by CIMAC/NCI, the plasma will be retrieved from storage and sent for testing.

9.8.5.2 Site Performing Correlative Study

This correlative study will be performed through the CIMAC network.

9.8.6 *TCR-Seq – Exploratory/Ancillary Laboratory Correlative Study*

Sequencing of the CDR3 variable region of the beta chain of the T cell receptor has been used for many years as a metric of T cell repertoire diversity and clonality. Although this method is not able to predict the specificity of T cells solely based on TCR nucleotide/amino-acid usage, it is a sufficient surrogate to detect specific clonal expansions or contractions, entropy, and tracking of clones, based on extensive available literature. Because of Adaptive Biotech's dominance and pioneering work in this field, we propose to use Adaptive technologies via the CIMAC network, for TCRseq on DNA from tissue and, pending the results on tissue, for TCRseq on DNA from PBMCs.

The assay is expected to yield information about changes in T cell repertoire from baseline to post-treatment, as well as to differences observed based on combinations in each study arm. Importantly, this assay will gain more functional insight if it is also performed in parallel at the tumor tissue site, to establish clones that appear there and that are also in circulation, in order to track their evolution over treatment arms in the periphery.

9.8.6.1 Specimen(s) and Processing at the EET Biobank

Archival FFPE if available, formalin-fixed tissue at Baseline, C1W4, and Progression time points will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank. When the assay labs are ready to perform the assays, sections will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed for DNA and RNA co-extraction.

DNA will be banked in a stock vial and stored in a -80°C freezer until distribution for testing. Nucleic acid from archival FFPE will be used for WES/RNAseq (MoCha) while all other specimens will be apportioned between MoCha and (for TCRseq, if specimen remains) CIMAC/Adaptive.

Blood collected in NaHep (green top) tubes at Cycle 1 Day 1 (before protocol treatment), on day 1 of cycle 2 and at or after the time of progression (end of treatment visit) will be used for this study.

Upon receiving the sodium heparin green-top tubes from the collection site, the biorepository will pool all samples from a blood draw at one timepoint and prepare plasma and PBMCs following a Ficoll-Paque protocol as outlined in the CIMAC umbrella protocol. Plasma is stored in a -80°C freezer and PBMCs are stored in a liquid nitrogen vapor phase freezer until distribution.

At the end of the study, when a request is made by CIMAC/NCI, the EET Biobank will co-extract DNA and RNA from the PBMCs and ship DNA from tissue and PBMCs for TCR sequencing according to CIMAC specifications to be provided at that time as well as to MoCha for WES/RNAseq testing.

9.8.6.2 Site Performing Correlative Study

This correlative study will be performed using Adaptive Biotechnologies through the CIMAC network.

9.8.7 *cfDNA – Exploratory/Ancillary Laboratory Correlative Study*

Cell-free DNA (cfDNA) analyses will be performed on blood samples from the Cycle 1 Day 1, Cycle 2 Day 1, and progression timepoints.

9.8.7.1 Specimen(s) and Processing at the EET Biobank

Whole blood collected in Streck cfDNA tubes will be centrifuged to separate plasma. Following plasma processing, DNA will be processed from blood at Cycle 1 Day 1. At C2D1 and Progression, plasma and buffy coat will be processed. Plasma and buffy coat aliquots will be stored in a -80°C freezer until distribution for analysis.

9.8.7.2 Site Performing Correlative Study

The Broad Institute (address below), working with CIMAC, will perform the cfDNA analyses.

The Broad Institute
Attn: Samples Lab
27 Blue Sky Drive
Burlington, MA, 01803

9.9 Biomarker Table:

Note for participating sites: Please see Section 9.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in protocol and Purpose	Specimen Type	Timepoints of Analysis	M/O Specimen Collection	Assay Lab
1	Serial TIL analysis	Multiplex IHC CLIA: N	Integrated Aim: Effect of MEK inhibition on CD8+ T cell infiltration	FFPE Tissue	1. Archival[i] (if Baseline not available) 2. Baseline 3. Cycle 1: Week 4 4. Progression[ii]	M (O for Progression)	Mt. Sinai CIMAC
2	PD-L1	IHC (CLIA: N)	Exploratory Aim: Assess the impact of therapy on PD-L1 expression within the tumor microenvironment	FFPE Tissue	1. Archival[i] 2. Baseline	M (O for progression)	Mt. Sinai CIMAC
3	WES	WES (CLIA: N)	Exploratory Aim: Confirmation of Expression of Neoantigens and Characterization of the Tumor Microenvironment	FFPE Tissue	1. Archival 2. Baseline 3. Progression	M	MoCha
4	RNAseq	RNAseq (CLIA: N)	Exploratory Aim: Confirmation of Expression of Neoantigens and Characterization of the Tumor Microenvironment	FFPE Tissue	1. Archival 2. Baseline 3. Cycle 1: Week 4 4. Progression	M	MoCha
5	TCRseq	Adaptive CLIA: N	Exploratory Aim: TCR clonality changes upon treatment	FFPE Tissue	1. Archival[i] 2. Baseline 3. Cycle 1: Week 4 4. Progression[ii]	M (O for progression)	Adaptive in collaboration with CIMAC
1	Immune Cell Profiling	CyTOF CLIA: N	Exploratory Aim: Quantify population frequencies of major immune subsets and markers of immune activation or suppression	PBMC from blood in NaHep	1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Progression	M	Mt. Sinai CIMAC
2	Plasma Soluble Analytes	Olink CLIA: N	Exploratory Aim: Quantification and correlation of cytokine levels	Plasma from blood in NaHep	1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Progression	M	Mt. Sinai CIMAC
3	Grand Serology	ELISA CLIA: N	Exploratory Aim: Antibody profiling, to measure changes in known tumor antigen-specific antibody responses	Plasma from blood in NaHep	1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Progression	M	Mt. Sinai CIMAC
4	WES (germline)	WES CLIA: N	Exploratory Aim: Germline control for tumor sequencing	DNA from blood in Streck cfDNA tubes	Cycle 1 Day 1	M	MoCha
5	TCRseq	Adaptive CLIA: N	Exploratory Aim: TCR clonality changes upon treatment	PBMC[iii] from blood in NaHep	1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Progression	M	Adaptive in collaboration with CIMAC
6	cfDNA	CLIA: N	Exploratory Aim: ctDNA changes upon treatment	Plasma from blood in Streck cfDNA tubes	1. Cycle 1 Day 1 2. Cycle 2 Day 1 3. Progression	M	The Broad Institute in collaboration with CIMAC

i. Any archival tumor specimens taken prior to the patient's initial treatment with a PD-1 or LD-L1 inhibitor should be submitted, when available
ii. Biopsies at progression are optional
iii. TCRseq and RNAseq may also potentially be performed in PBMCs, pending the results of these assays in tissue

10. STUDY CALENDAR

Physical examinations and laboratory testing may be completed up to 7 days prior to Day 1 dosing. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Patients receiving atezolizumab will be assessed for pulmonary signs and symptoms on physical examination as well as imaging throughout the study.

	Pre-Study	Cycle 1 (28 Days)			Cycle 2 and beyond (28 Days)	Off Treatment[L]
		Day 1	Day 15	Day 22	Day 1	
Visit window[A]	*-28 to -1*	*+/-2*	*+/-2*	*+/-7*	*+/-2*	*+/-10*
Informed consent	X					
Demographics	X					
Medical history[B]	X					
Concomitant medications	X	X			X	
Physical exam[C]	X	X	X		X	X
Vital signs[D]	X	X	X		X	X
Height	X					
Weight	X	X			X	X
Performance status	X	X			X	X
CBC w/diff[E]	X	X	X		X	X
Serum chemistry[E]	X	X	X		X	X
Amylase and lipase	X	X			X	X
Coagulation (INR and aPTT)	X					
Thyroid function test[F]	X				X	
EKG (electrocardiogram)	X					
B-HCG[G]	X					
CPK	X	X			X	
ECHO or MUGA	X	1 month after first dose, then every 3 months on cobimetinib (see [M])				
Ophthalmologic exam[H]	X	Every 2 months for 1 year, then every 6 months while on cobimetinib (see [N])				
Adverse event evaluation		X	X		X	X[O]
Tumor measurements[I]	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease if possible.				X
Archival tumor sample (when available)	X					
Tumor biopsy[J]	X			X		X[P]
Peripheral blood for research[K]		X[K]			X[K]	X[K]
Atezolizumab		X			X	
Cobimetinib		[----Oral daily in the morning on days 1–21 of a 28-day cycle----]				
Medication Diary		X			X	

A: Longer durations to be approved by the Study Principal Investigator.
B: Includes history of lung disease, HIV, hepatitis B or C infection, and complete cancer history, including primary site of cancer, gross location of primary tumor, secondary sites of cancer, histology, histologic grade, date of initial diagnosis, date of metastatic diagnosis, and prior cancer therapy regimens.
C: Complete physical exam will be completed at baseline; focused physical examinations will be conducted thereafter. Physical examinations should be performed within a window of up to 7 days prior to dosing on days 1 and 15 of cycle 1 and day 1 for all subsequent cycles.
D: Temperature, respiration rate, blood pressure, pulse, and pulse ox should be taken prior to the administration of atezolizumab
E: Serum Chemistry should include Glucose, Calcium, Sodium, Potassium, CO2, Chloride, BUN, Creatinine, Alkaline phosphatase, Alanine amino transferase (ALT), Aspartate amino transferase (AST), Bilirubin, Albumin, and Total Protein. Labs may be collected within a window of up to 7 days prior to dosing. Initial screening bloodwork does not need to be repeated if performed within 7 days of C1D1.
F: Free T3/T4 should be checked reflexively if TSH is abnormal
G: Serum or urine pregnancy (women of childbearing potential only). For women with a mildly elevated B-HCG who in the opinion of the investigator are not pregnant, a vaginal ultrasound must be obtained to confirm that the participant is not pregnant in order to enroll on this study.
H: In addition to scheduled evaluations, any patients with ocular symptoms occurring during study treatment should be examined by an ophthalmologist as needed
I: Baseline scans must be done ≤ 4 weeks prior to randomization. Tumor measurement will be performed with contrast CT chest/abdomen/pelvis though pelvis can be excluded if there is no known disease in the pelvis. Non-contrast CT chest/abdomen/pelvis or CT Chest and MRI Abdomen/pelvis will be performed in subjects with contraindications or intolerance to contrast dye, though pelvis can be excluded if there is

no known disease in the pelvis. Imaging will be repeated every 8 weeks, irrespective of dosing schedule or treatment delays. With the off study visit, scans do not need to be repeated if a scan has been performed within 8 weeks.
J: Mandatory biopsies are performed prior to cycle 1, day 1 and in week 4 of cycle 1, provided the biopsy is felt to be safe and feasible (section 9). A biopsy at the time of progression is optional.
K: Peripheral whole blood for research will be collected in NaHep (green top) tubes 20 mL and 2 10-mL cfDNA Streck tubes (section 9). Baseline collection will be prior to dosing; this can be done at screening or on cycle 1, day 1. Subsequent blood draws include cycle 2, day 1 and at the time of progression or at the off study visit. For additional details, see section 9.
L: Off-Treatment evaluations will be completed 4 weeks after meeting at least one of the criteria listed in section 5.3.
M: Evaluation of LV function by either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) 1 month after first dose, then every 3 months while on cobimetinib (visit window +/-7 days);
N: Ophthalmologic examination at baseline, then every 2 months for 1 year, then every 6 months while on cobimetinib (visit window +/- 14 days); Eye exam should include retinal exam, slit lamp exam, and visual fields (preferably Goldmann Visual Field if available) for evidence of retinal pathology and other abnormalities.
O: Adverse events will be assessed at least 30 days after the last dose of either study agent. For patients removed due to unacceptable toxicity, they will be followed until resolution of the adverse event.
P: Optional biopsy at progression

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer *et al*., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab and cobimetinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may not be considered measurable unless there is evidence of progression in the irradiated site.
Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1

to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment 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 follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are

superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment

until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Overall Survival (OS)

OS is defined as the duration of time from start of study treatment to time of death.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During this Phase 2 study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.
To ensure safety of this combination in this specific patient population, the Protocol Principal Investigator will review all SAEs submitted for enrolled patient every month. If there are any unexpected grade 4 or higher toxicities or if more than 1 out of 3 patients discontinue treatment for toxicity, the Protocol Principal Investigator will initiate a teleconference with all site PI's and the CTEP Medical Officer(s) to review the findings and determine whether the study should continue in its current form or be amended or discontinued.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin), the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned

on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

In addition, the lead Principal Investigator will have at least monthly conference calls with the site Study Investigators and study teams to review accrual, progress, adverse events, and unanticipated problems.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

Not applicable.

12.4 Collaborative Agreements Language

The agents supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-

Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The purpose of this phase II trial is to determine whether treatment with atezolizumab plus cobimetinib has sufficient activity against NSCLC tumors resistant or refractory to prior PD-1 or PD-L1 therapy to warrant its further development. The primary objective of this study is to evaluate durable response rate to therapy. Secondary objectives include the overall response rate, the duration of response, the progression-free survival (PFS), the overall survival (OS) and the grade 3 and 4 toxicity rate in patients of atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy. The final study analysis will be based on patient data collected through study discontinuation.

The grading and reporting of gastrointestinal toxicity, hepatic toxicity, dermatologic toxic, pulmonary toxicity, potential eye toxicity, cardiac toxicity, rhabdomyolysis and hemorrhage are defined in Sections 6-7, and all patients who receive any amount of the study drug will be evaluable for toxicity

13.2 Sample Size/Accrual Rate

The sample size for each cohort will be determined by the Simon's two-stage design rules. It will require a minimum of 9 and 24 evaluable patients in both cohort I and II. The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative at 0.25. In the first stage, 9 patients will be accrued. If there are no responses in these 9 patients, the study will be stopped. Otherwise, 15 additional patients will be accrued for a total of 24. The null hypothesis will be rejected if 3 or more responses are observed in 24 patients. This design yields a type I error rate of 10% and power of 90% when the true response rate is 0.25.

The Simon two-stage design will employ any response using RECIST version 1.1 criteria *except* for the expansion, responses do not need to be confirmed. Duration or durability of that response will not impact the Simon two-stage design. However, the final analysis (Section 13.4) will assess durable response rate using RECIST version 1.1 criteria. A durable response is defined as a response meeting RECIST version 1.1 criteria in a patient whose treatment duration was of at least 6 months.

Note: Cohort I will include only patients with *KRAS* mutant NSCLC. If Cohort I is positive, with at least one durable response (treatment duration of at least 6 months), then Cohort II will open to enrollment. Cohort II will include only patients without a *KRAS* mutation (*KRAS* wild type).

Enrollment and major protocol violations, study treatment administration, and reasons for patient discontinuations from the study will be described and listed or summarized. Demographic and baseline characteristics, such as sex, race, and ethnicity, and a rationale for selection of subjects, will be summarized.

13.3 Stratification Factors

There is no stratification in this non-randomized study.

13.4 Analysis of Endpoints

Primary endpoints. The primary analysis of evaluating durable response rate with atezolizumab plus cobimetinib in patients with metastatic non-small cell lung cancer (NSCLC) resistant or refractory to prior PD-1 or PD-L1 therapy will be presented with descriptive statistics. For each cohort (*KRAS* mutant and *KRAS* wild type), if the cohort expands to the second stage, the analysis will examine the durable response rate. A durable response is defined as a response meeting RECIST version 1.1 criteria in a patient whose response duration was of at least 6 months. The durable response rate will be descriptive given the small sample size. If 3 or more durable responses are seen in 24 patients (each cohort will be analyzed separately), the null hypothesis will be rejected and the combination will warrant further investigation. If 3 or more transient responses are seen but < 3 durable responses are seen, the null hypothesis will not be rejected. We will use chi-square statistics to describe and analyze results with ethnic categories and racial categories, respectively.

Secondary endpoints. The overall response rate will be descriptive given the small sample size. For analysis, we will employ RECIST version 1.1 criteria. We will use chi-square statistics to describe and analyze results with ethnic categories and racial categories, respectively. For lifetime data analyses, Kaplan-Meier estimates will be used to describe the PFS and OS with atezolizumab plus cobimetinib in patients with metastatic NSCLC resistant or refractory to prior PD-1 or PD-L1 therapy. The association of PFS and survival with biomarkers will be assessed using Cox regression model with model adequacy assessment. The analysis of biomarkers will also be descriptive given the limited sample sizes. Categorical data analysis methods such as Chi-square will be used to evaluate the correlation of baseline tumor mutation burden to response to therapy. Regression and correlation will be used for assessing the association between continuous variables such as tumor burden and other markers and patient characteristics such as age.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

The safety analysis will be performed in all subjects who receive any amount of study drug. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after at least 1 dose of study treatment may be required for inclusion in the analysis of a specific safety parameter (e.g., lab shifts from baseline). A complete list of all AE data will be provided along with an assessment of NCI CTCAE version 5.0 grade and relationship to study drug. The incidence of AEs will be tabulated by subgroups of interest (e.g. grade 3 or higher, organ class, relationship to study drug). For analyses at the individual level, the highest grade and relationship to study drug will be assumed if multiple events have occurred. Toxicity will be tabulated by type and grade and will be summarized with descriptive statistics. Other safety data will be assessed in

terms of physical examination, clinical chemistry, hematology, vital signs, and EKGs. Negative binomial regression and Cox proportional hazards models will be used to assess the rate of AE and time to first toxicity, respectively.

13.5.2 Evaluation of Response

All subjects who have completed at least one dose of therapy will be included in the evaluation of response. Each patient will be assigned of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease.

The objective response rate is defined as the proportion of response evaluable subjects who have a complete response (CR) or partial response (PR) using RECIST 1.1 criteria at any time during the study. The evaluable population is as defined for the primary endpoint. Response rates will be reported for each group along with exact confidence intervals.

13.5.3 Evaluation of Correlative Aims

Correlative studies will be performed:

- To measure the baseline expression and on treatment expression of PD-L1 and correlate these variables with treatment response.
- To measure the baseline levels of immune markers including CD8+ T effector cells and CD4+FoxP3+ T regulatory cells, and tumor infiltrating lymphocytes (TILs), major histocompatibility complex (MHC) class I and II expression, and natural killer (NK) cell receptors and ligands expression and correlate these variables with treatment response and toxicity.
- To characterize changes in the immune markers described above after treatment
- To measure changes in circulating immune suppressor cells (MDSC, Treg) in peripheral blood by flow cytometry and test for association with response to therapy.

The overarching aim of these studies is to establish baseline levels for, and measure changes in immunological pathways after treatment. Little is known about baseline levels for these variables in cholangiocarcinoma, let alone changes after treatment, and if the primary and secondary aims are successful, these investigations will establish a biological foundation on which to build in follow up studies.

Immunological variables will be examined in plots and summary statistics, to characterize distributions, identify outliers and other potential problems in the data. Joint exploratory analysis will identify associations and potential interactions. Variables may be transformed on the basis of these investigations, to reduce skewness, minimize the influence of outliers and/or to regularize relationships between predictors and response for better model fit. Exploratory analysis of the molecular markers, including visualizations and statistical summaries such as hierarchical cluster analysis, heat maps, multidimensional scaling, and principle component analysis will offer important views of the structural characteristics of the expression data.

Response will be described categorically, and associations between response and immunological variables will be characterized, in each arm, using multivariate logistic regression models, with adjustment for clinical and pathological co-variates that may be associated with response. Estimated effects will be reported with standard errors and confidence intervals.

While the primary focus is on CD8+ lymphocyte density, additional markers will be included in the panel including CD3, FOXP3, CD20, CD66b, PD-1, PD-L1, DC-LAMP, and HLA-DR. The method used can accommodate 8 markers routinely but if tissue integrity is good, additional markers can be added.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG INFORMATION HANDOUT & WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drugs, atezolizumab (trade name Tecentriq®), and cobimetinib (trade name Cotellic®). This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

- The patient is on an immunotherapy clinical trial, designed to help the immune system attack cancer. There is a risk of developing autoimmune side effects from the study drugs, and these autoimmune side effects may be serious and challenging to diagnose. Examples of autoimmune side effects previously observed in clinical trials of immunotherapy drugs include:
    - Endocrinopathies (e.g., hypothyroidism, adrenal insufficiency, panhypopituitarism, new onset type 1 diabetes)
    - Inflammation of various organs (colitis, pneumonitis, hepatitis, myocarditis)
    - Rheumatologic diseases (for example, rheumatoid arthritis, myositis)

  When evaluating this patient for an acute medical complaint, please consider that the patient may be experiencing an immune-related adverse event.

- Cobimetinib is a substrate of substrate of CYP3A4 (major). Therefore, cobimetinib is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.
- Cobimetinib is a substrate of efflux transporter P-glycoprotein (P-gp). Drugs that inhibit P-gp may increase cobimetinib concentrations.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Atezolizumab (trade name Tecentriq®) and cobimetinib (trade name Cotellic®) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Cobimetinib (trade name Cotellic®) must be used very carefully with other medicines that use certain liver enzymes to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A4.

- Please be very careful! Over-the-counter drugs (including some herbal supplements such as St. John's wort) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drugs atezolizumab and cobimetinib. This clinical trial is sponsored by the NCI. Cobimetinib may interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	Cobimetinib interacts with a specific liver enzyme called CYP3A4 and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A4. ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX C PATIENT STUDY DRUG TABLET DIARY - COBIMETINIB

PATIENT ID	
CYCLE NUMBER	

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take cobimetinib. Each cycle of therapy is 4 weeks (28 days).
2. Take your dose of cobimetinib at about the same time each morning for the first 21 days. Do not take cobimetinib on days 22 through 28.
3. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you miss taking your dose and remember within 1 hour of your scheduled dose, you may take it late. If it has been more than 1 hour, do not make up the dose; resume dosing with the next scheduled dose. If vomiting occurs, do not make up the dose; resume dosing with the next scheduled dose.
5. Take cobimetinib tablets orally in the morning with or without food. The tablets should be swallowed whole and must not be crushed or broken.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ *SB 9:30 am*
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of Daily Dose	# of Tablets Taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				

Day	Date	Time of Daily Dose	# of Tablets Taken	Comments
15				
16				
17				
18				
19				
20				
21				
22		Do not take cobimetinib on these days.		
23				
24				
25				
26				
27				
28				

Participant's Initials	Date

Physician's Office will complete this section:

1. Total number of tablets taken this month (each size)

2. Physician/Nurse/Data Manager's Signature/Date

APPENDIX D TISSUE BIOPSY VERIFICATION

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.
Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Primary Metastatic

Time point (circle one): Baseline Cycle 1, Week 4

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

_____
Clinician Signature Date

_____
Clinician Printed Name

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.