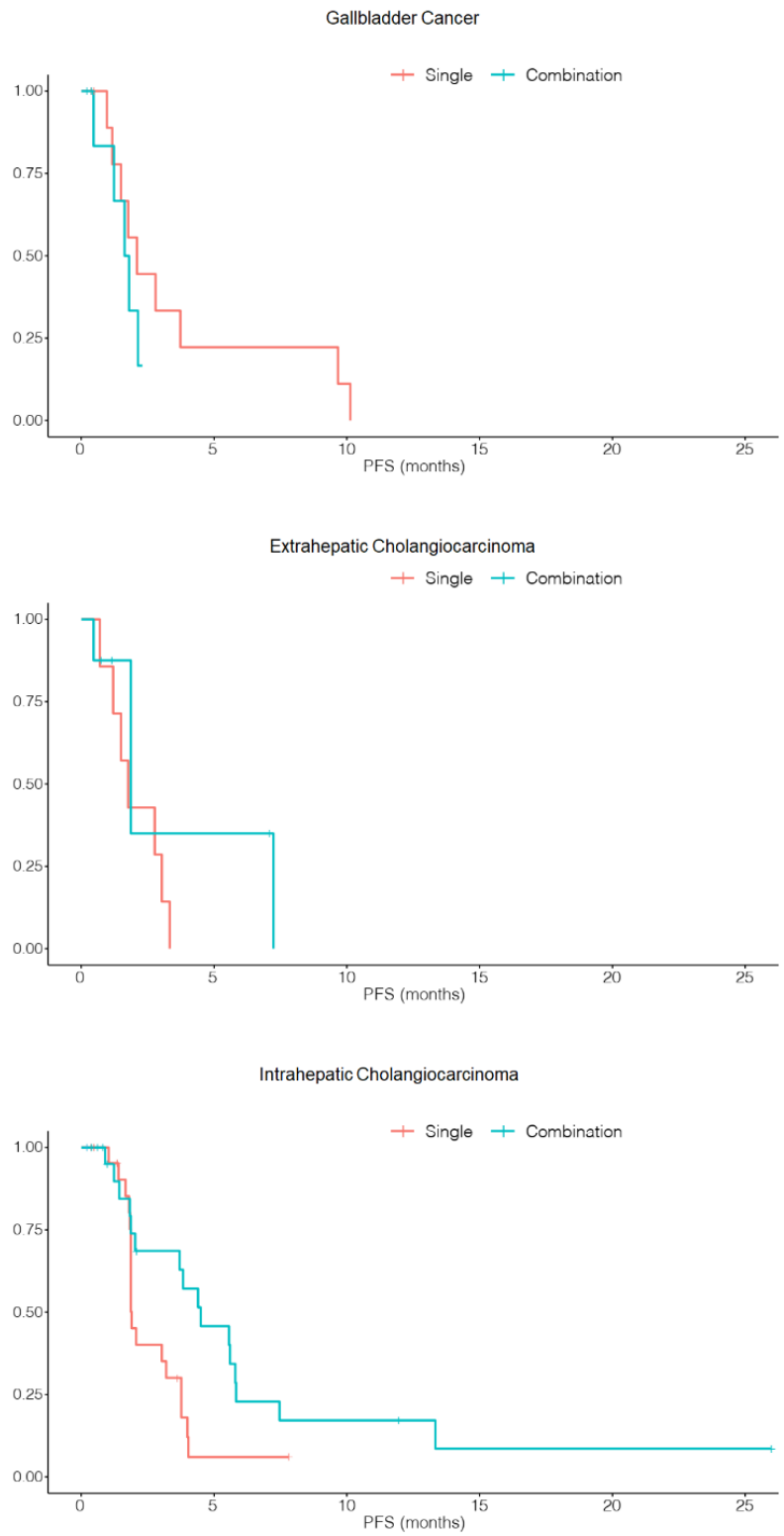
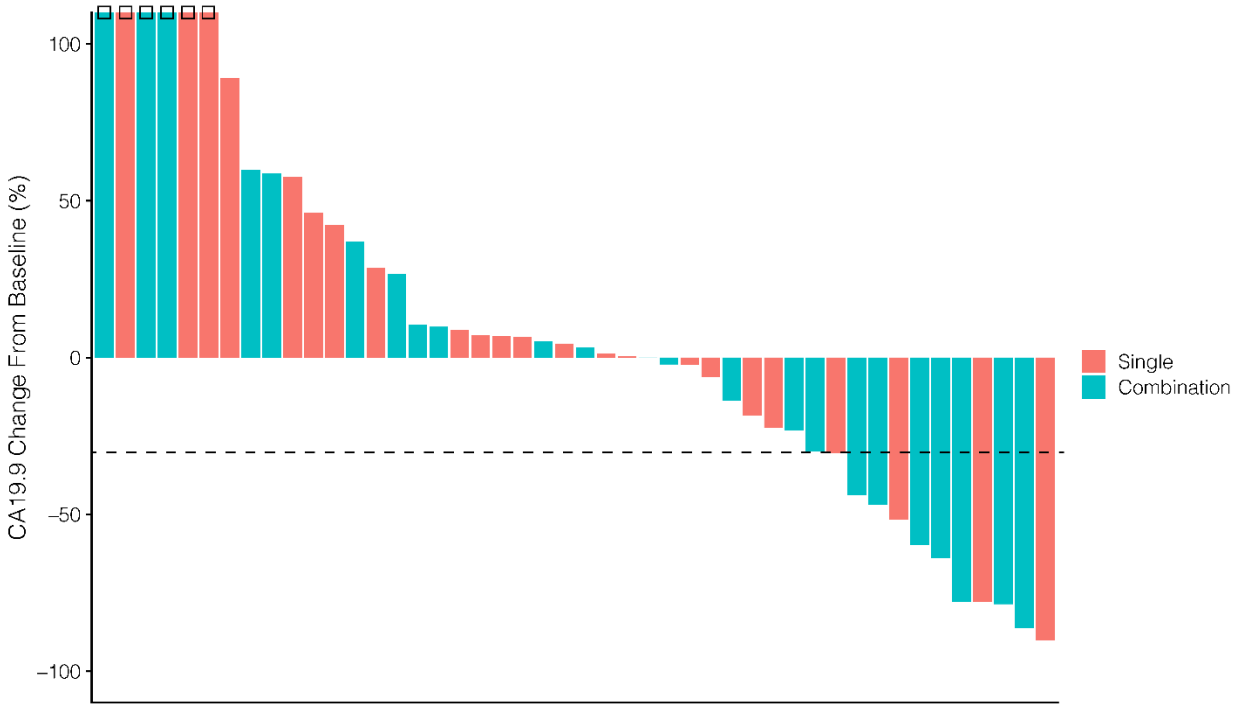
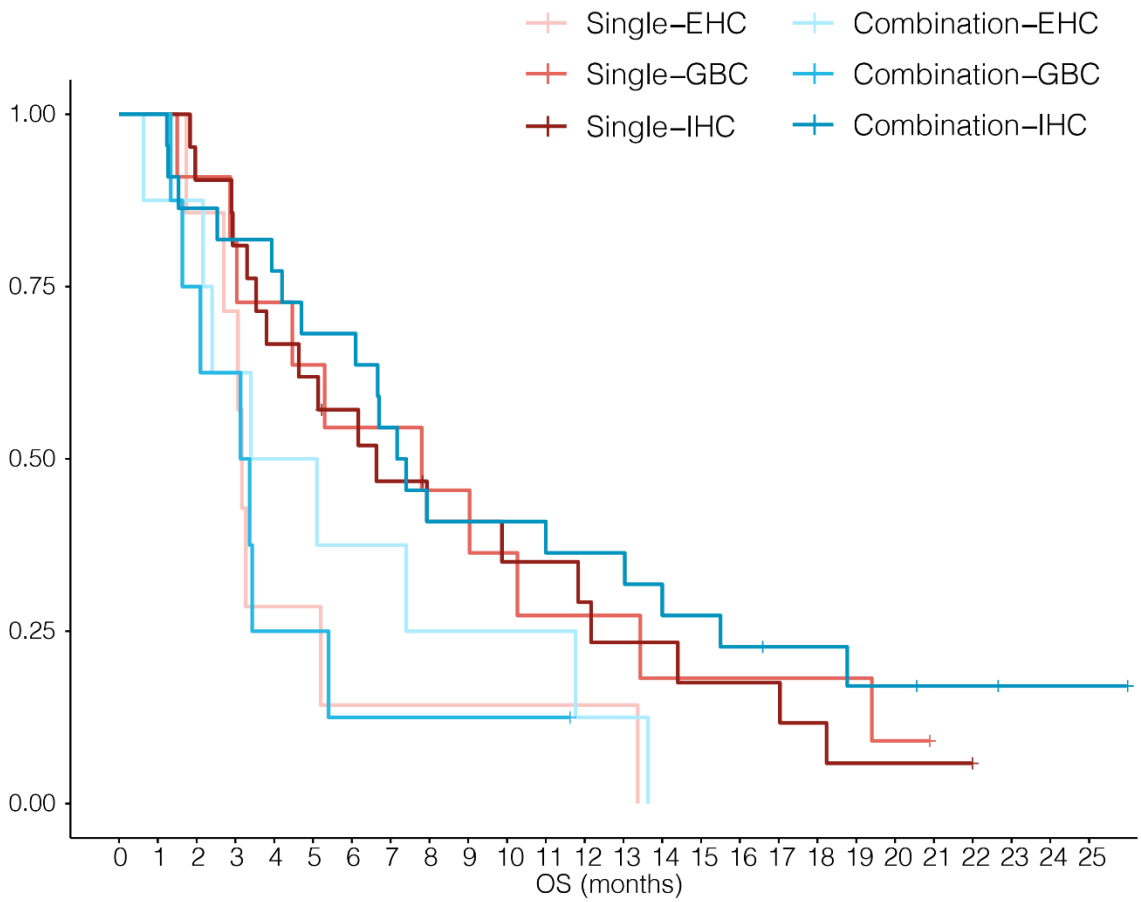
Supplemental Figure 1
Progression free survival, stratified by treatment group and primary anatomical disease subgroup.



Supplemental Figure 2
Change in CA19-9 levels with treatment for all patients with an elevated CA19-9 level at baseline.



Supplemental Figure 3
Overall survival, by treatment group and primary disease site

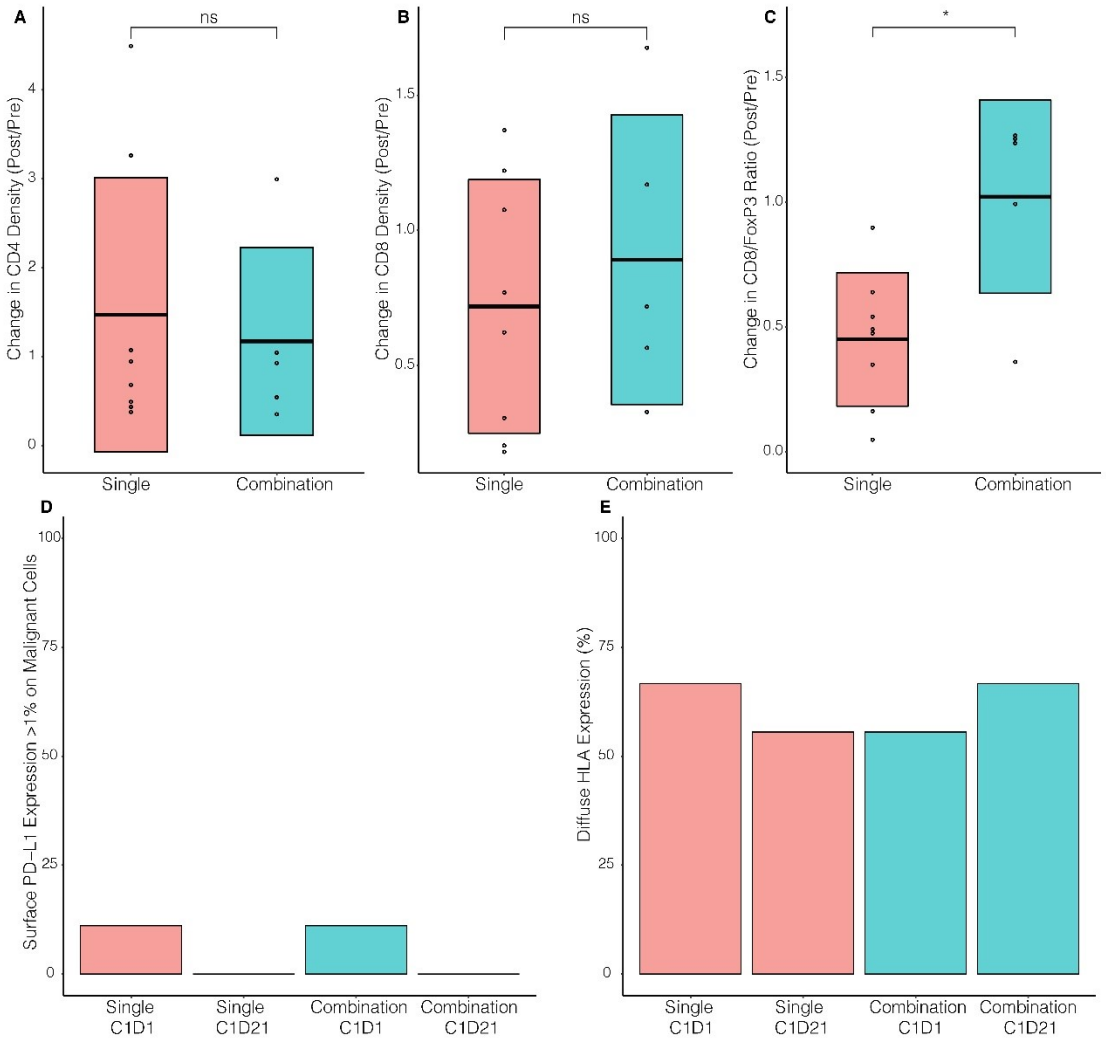


Number at risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
ARM A–EHC	7	7	6	5	2	2	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
ARM A–GBC	11	11	10	9	8	7	6	6	5	5	4	3	3	3	2	2	2	2	2	2	1	0	0	0	0	0
ARM A–IHC	21	21	19	17	14	13	11	9	7	7	6	6	5	4	4	3	3	3	2	1	1	1	0	0	0	0
ARM B–EHC	8	7	7	5	4	4	3	3	2	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0
ARM B–GBC	8	8	6	5	2	2	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ARM B–IHC	22	22	19	18	17	15	15	12	9	9	9	9	8	8	7	6	5	4	4	3	3	2	2	1	1	1

Time

Supplemental Figure 4
Changes in the tumor immune microenvironment with treatment, assessed by immunohistochemistry, in the subset of patients with accessible serial biopsies.



Supplementary Table 1

4 Month PFS				
Arm	PFS	std.err	95% LCB	95% UCB
ARM A	0.094	0.051	0.033	0.271
ARM B	0.446	0.091	0.299	0.666
6 Month PFS				
Arm	PFS	std.err	95% LCB	95% UCB
ARM A	0.094	0.051	0.033	0.271
ARM B	0.223	0.079	0.111	0.446
12 Month PFS				
ARM A	0	NA	NA	NA
ARM B	0.134	0.068	0.049	0.362

Supplementary Table 2

Antibody	Fluorophore	Manufacturer	Clone
CD45	PerCP	BioLegend	HI30
CD3	BV510	BioLegend	UCHT1
CD4	PE/Cy5	Invitrogen	RPA-T4
CD8	APC/Cy7	BioLegend	SK1
LAG3	AlexaFluor700	Invitrogen	3DS223H
BTLA	PE/Cy7	BioLegend	MIH26
VISTA	APC	Invitrogen	B7H5DS8
TIM3	SuperBright600	Invitrogen	F38-2E2

SUMMARY OF CHANGES – Protocol

For Protocol Amendment to Protocol Dated: April 4, 2018
NCI Protocol #: 10139
Local Protocol #: TBD

NCI Version Date: April 4, 2018
Protocol Date: April 4, 2018

I. Changes to the Protocol:

#	Section	Comments
1.	Title Page	The protocol version date has been updated to 04/04/2018.
2.	3.1.1	Eligibility criteria has been clarified to indicate that only patients with metastatic or unresectable disease are eligible
3.	3.2.22	For study exclusion criteria, symptomatic CHF is defined as New York Heart Association CHF Class II or higher disease.
4.	10	Adverse events will be assessed at least 90 days after the last dose of either study agent.
5.	5.3.1	For patients treated past progression, a follow-up scan is now required 6-8 weeks following first progression. The study calendar was also updated to make this requirement.
6.	5.3.1	Section 5.3.1 has been updated to include the following criteria for treatment past progression: no evidence of clinical deterioration and no evidence of progressive disease at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
7.	10	Clarified that baseline and periodic transthoracic echocardiograms or multiple-gated acquisition scans and ophthalmology exams will be performed are for all patients at baseline, but only for study arm B (cobimetinib-treated patients only) thereafter.
8.	10	Permit Humphrey Visual Field testing as an alternative to Goldmann Visual Field testing.
9.	10	Clarified the study window for radiologic scans and research bloods.
10.	3.2.13	Clarified that only strong inhibitors or inducers of CYP3A are an exclusion criteria, as discussed in section 5.2.3.

#	Section	Comments
11.	4.1	Updated section 4.1 in accordance with the new Registration and Credentialing Repository language.
12.	4.2 4.2.2	Updated the language in section 4.2 and 4.3 to reflect the current CTEP template. Updated site registration requirements.
13.	12.2	Updated the language in section 12.2 and 4.3 to reflect the current CTEP template. Updated data reporting requirements.
14.	N/A	Minor formatting and editorial changes were made throughout the protocol.
15.	4.3.2 4.3.3	Updated patient registration requirements.

NCI Protocol #: 10139

Local Protocol #: ETCTN10139

ClinicalTrials.gov Identifier: *NCT03201458*

TITLE: A Randomized Phase 2 Study of Atezolizumab in Combination with Cobimetinib versus Atezolizumab Monotherapy in Participants with Unresectable Cholangiocarcinoma

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NCI-Supplied Agents:
Atezolizumab (MPDL3280A; NSC 783608; Tecentriq);
Cobimetinib (RO5514041; GDC0973; XL518; NSC 781257; Cotellic)

IND #: 131657 RO5514041, GDC0973
IND Sponsor: *DCTD, NCI*

Protocol Type / Version # / Version Date: *[Original / Version 1 / 4/1/2017]*

Protocol Type / Version # / Version Date: *[Revised / Version 1 / 07/13/2017]*

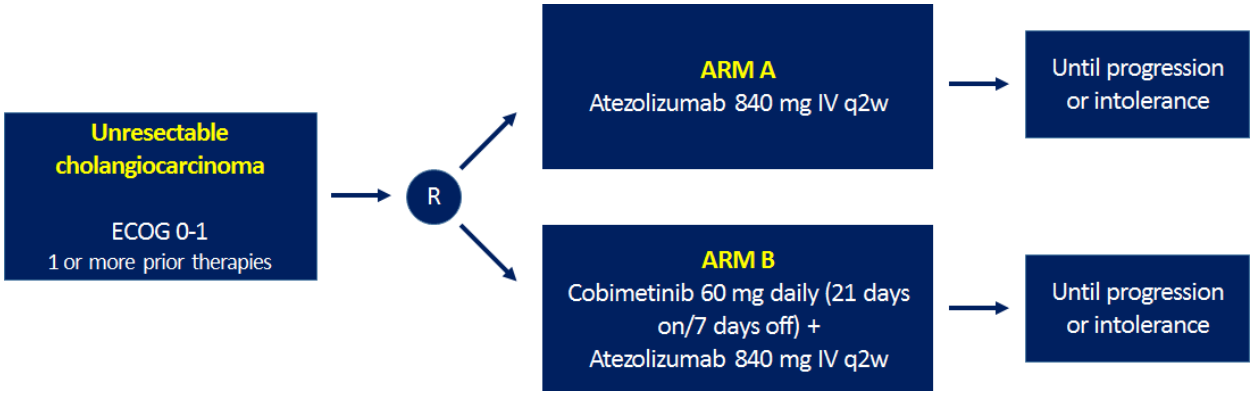
Protocol Type / Version # / Version Date: *[Revised / Version 1 / 08/15/2017]*

Protocol Type / Version # / Version Date: *[Revised / Version 1 / 09/27/2017]*

Protocol Type / Version # / Version Date: *[Revised / Version 2 / 02/04/2018]*

Protocol Type / Version # / Version Date: *[Revised / Version 3 / 04/04/2018]*

STUDY SCHEMA



- This is an open-label randomized phase 2 trial evaluating atezolizumab monotherapy and cobimetinib in combination with atezolizumab.
- Each treatment cycle = 28 days
- Patients randomized to Arm A will receive treatment with atezolizumab 840 mg IV every 2 weeks.
- Patients randomized to Arm B will receive oral cobimetinib 60 mg daily (21 days on/7 days off) plus atezolizumab 840 mg IV every 2 weeks. Therapy on either treatment arm will be continued without interruption until progression or intolerance to therapy.
- For all patients, imaging scans will be performed at baseline and every 8 weeks thereafter, irrespective of the treatment schedule.

TABLE OF CONTENTS

STUDY SCHEMA....3

1. OBJECTIVES....6
   1.1 Primary Objectives....6
   1.2 Secondary Objectives....6
   1.3 Correlative Objectives....6

2. BACKGROUND....7
   2.1 Study Disease(s)....7
   2.2 CTEP IND Agents....7
   2.3 Rationale....13
   2.4 Correlative Studies Background....14

3. PATIENT SELECTION....16
   3.1 Eligibility Criteria....16
   3.2 Exclusion Criteria....17
   3.3 Inclusion of Women and Minorities....20
   3.4 Stratification factors....22

4. REGISTRATION PROCEDURES....23
   4.1 Investigator and Research Associate Registration with CTEP....23
   4.2 Site Registration....23
   4.3 Patient Registration....25
   4.4 General Guidelines....27

5. TREATMENT PLAN....27
   5.1 Agent Administration....27
   5.2 General Concomitant Medication and Supportive Care Guidelines....30
   5.3 Duration of Therapy....32
   5.4 Duration of Follow Up....33
   5.5 Criteria for Removal from Study....33

6. DOSING DELAYS/DOSE MODIFICATIONS....34
   6.1 Atezolizumab....34
   6.2 Cobimetinib....49
   6.3 Management of Cobimetinib plus Atezolizumab−Associated Adverse Events of particular concern....50

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS....63
   7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)....63
   7.2 Adverse Event Characteristics....69
   7.3 Expedited Adverse Event Reporting....69
   7.4 Routine Adverse Event Reporting....72
   7.5 Secondary Malignancy....73

7.6 Second Malignancy 73

8. PHARMACEUTICAL INFORMATION 73
8.1 CTEP IND Agent(s) 73

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES 79
9.1 Hypotheses and background 79
9.2 Preliminary data 79
9.3 Methods 80

10. STUDY CALENDAR 87

11. MEASUREMENT OF EFFECT 89
11.1 Antitumor Effect – Solid Tumors 89

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS 96
12.1 Study Oversight 96
12.2 Data Reporting 96
12.3 CTEP Multicenter Guidelines 98
12.4 Collaborative Agreements Language 98

13. STATISTICAL CONSIDERATIONS 100
13.1 Study Design/Endpoints 100
13.2 Sample Size/Accrual Rate 101
13.3 Stratification Factors 101
13.4 Analysis of Secondary Endpoints 102
13.5 Reporting and Exclusions 102

14. REFERENCES 104

APPENDIX A PERFORMANCE STATUS CRITERIA 106

APPENDIX B PATIENT DRUG INFORMATION HANDOUTS AND WALLET CARDS 107

APPENDIX C STUDY CHECKLIST FOR CTEP-SUPPORTED EARLY PHASE TRIALS WITH BIOMARKER ASSAYS AND BIOASSAY TEMPLATES 113

APPENDIX D IMMUNE-RELATED RESPONSE CRITERIA 116

APPENDIX E PATIENT MEDICATION DIARY - COBIMETINIB 118

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the progression free survival (PFS) of patients receiving atezolizumab monotherapy and cobimetinib in combination with atezolizumab for unresectable cholangiocarcinoma.

1.2 Secondary Objectives

1.2.1 To assess the overall survival (OS) of patients receiving cobimetinib in combination with atezolizumab and atezolizumab monotherapy for unresectable cholangiocarcinoma.
1.2.2 To determine the objective response rate (ORR), defined as complete plus partial response, of cobimetinib in combination with atezolizumab and atezolizumab monotherapy in patients with unresectable cholangiocarcinoma.
1.2.3 To assess the safety and tolerability of cobimetinib in combination with atezolizumab and atezolizumab monotherapy in patients with unresectable cholangiocarcinoma.
1.2.4 To determine the relationship between PD-L1 expression in tumor at baseline and on treatment, and response to treatment.

1.3 Correlative Objectives

1.3.1 To determine the effect of cobimetinib on CD8+ T cell infiltration in tumor.
1.3.2 To determine the effect of cobimetinib on T cell subpopulations systemically and in tumor, PD-1/PD-L1 expression on tumor, and MHC 1/2 expression.
1.3.3 To determine the effect of cobimetinib on markers of immune exhaustion and pro-apoptotic factors in CD8+ effector T cells.
1.3.4 To explore the effect of cobimetinib on local and systemic immune activation pathways and immune suppressive pathways through expression profiling.

2. BACKGROUND

2.1 Study Disease(s)

Cholangiocarcinoma refers to cancers of the bile duct that arise in the intrahepatic, perihilar, or distal (extrahepatic) biliary tree and is the second most common primary liver tumor. Cholangiocarcinoma is a relatively rare cancer, accounting for approximately 3 percent of all gastrointestinal malignancies (or approximately 3500 new cases per year in the US), although the incidence is increasing globally (Khan et al. 2008, Patel 2001, Siegel et al. 2016). A small subset of patients with cholangiocarcinoma can be cured with surgical resection, but the majority of patients have unresectable disease at the time of presentation. Overall survival for this disease (which includes resectable patients) is poor, with less than 5% of patients surviving to 5 years (Shaib & El-Serag 2004). The most commonly used frontline therapy in patients with unresectable cholangiocarcinoma and a good performance status is palliative gemcitabine plus cisplatin. No regimen has ever conclusively shown benefit in second line treatment of cholangiocarcinoma (Lamarca et al. 2014) and the current treatment guidelines do not provide a recommendation for second line therapy. Prior retrospective studies suggest that the progression-free survival of second-line chemotherapy is only 2-3 months (Lamarca et al. 2014, Rogers et al. 2014). Therefore, cholangiocarcinoma remains a key area of unmet medical need.

2.2 CTEP IND Agents

2.2.1 <u>Atezolizumab</u>

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, 2016). 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 locally advanced or metastatic urothelial carcinoma and as well as metastatic non-small cell lung carcinoma.

2.2.1.1 <u>Mechanism of Action</u>

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, 2016). Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21−89 years), body weight, gender, 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, 2016). 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), 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 Rationale

As a single agent, anti-PD-1 therapies are most effective in tumors with high levels of effector T cell infiltration and PD-L1 expression (Taube et al. 2014). PD-L1 is expressed in high number of cholangiocarcinomas at baseline and is associated with poor survival, which suggests that cholangiocarcinoma may be particularly sensitive to a strategy that tweaks the tumor microenvironment and immune cellular compartments (Suleiman et al. 2015) (Mody et al. 2016). Preliminary activity of anti-PD-1 therapy in this disease is supported by a phase 1B trial pembrolizumab (Keynote 028). This trial, which only enrolled patients with positive PD-L1 tumor expression, had 4/23 partial responses (17% ORR). Therefore, further investigation of immune checkpoint inhibitors in cholangiocarcinoma is warranted.

The MAPK/ERK signaling pathway is involved in the regulation of normal cell proliferation, survival and differentiation, and this pathway is often aberrantly upregulated in a wide number of human cancers including cholangiocarcinoma. The MEK 1/2 inhibitor MEK162 (ARRY-438162) was studied in cholangiocarcinoma in a phase 1 clinical trial; this study reported two objective responses including one complete response, as well as a 46% stable disease rate for a median duration of 5 months. Interestingly, no MAKP/ERK mutations were identified in either of the responders in this study. This study provided initial support for MEK inhibition in the treatment of cholangiocarcinoma. Preliminary signs of activity were also observed in studies of another MEK inhibitor, selumetinib (AZD6244, ARRY-142886), alone and in combination with gemcitabine and cisplatin in patients with cholangiocarcinoma (Bekaii-Saab et al. 2011), and additional efforts to advance MEK inhibitors in cholangiocarcinoma are ongoing.

While these preliminary clinical data provide a basis for studying MEK inhibitors and anti-PD-1 therapies individually cholangiocarcinoma, there is emerging preclinical data that the activity of MEK inhibitors and anti-PD-1 therapies may be synergistic, by modulating immune function and/or priming the tumor microenvironment. Several studies have demonstrated that MEK inhibitors upregulate the expression of MHC and downregulate certain immunosuppressive mechanisms within the tumor (Kakavand et al. 2015, Liu et al. 2015, Reddy et al. 2016). Additionally, Ebert and colleagues recently demonstrated that MEK inhibition may also directly

potentiate T-cell based anti-tumor immunity (Ebert et al. 2016). They demonstrated in an animal model that MEK inhibition can reverse T cell signal-driven apoptotic ''exhaustive'' T cell death within a tumor by blocking the upregulation of certain pro-apoptotic factors; this results in the accumulation of CD8+ T cells within tumors. In the aggregate, these data provide mechanistic rationale for combination treatment with a MEK inhibitor and an immunomodulator targeting PD-1.

The preliminary clinical data of combination therapy with a MEK inhibitor and an anti-PD-1 therapy has been encouraging. The MEK inhibitor cobimetinib and the PD-L1 inhibitor atezolizumab were recently studied in combination in a phase 1 study of mismatch repair proficient (MMR-p) colorectal carcinoma (Bendell et al. 2016). The combination of cobimetinib and atezolizumab was well tolerated and full dose escalation was achieved [cobimetinib 60 mg daily (21 days on/7 days off) plus atezolizumab 800 mg IV q2w]. While neither therapy has previously demonstrated activity in MMR-p colorectal carcinoma when used as monotherapy, the combination of these agents resulted in a 17% overall response rate (4/23 evaluable patients). Correlative work from this study demonstrated that treatment with cobimetinib resulted in increased PD-L1 expression, increased tumor infiltration with CD8 T-cells, and increased MHC I expression. These findings support the hypothesis that MEK inhibition can prime a cancer to become a checkpoint sensitive tumor.

In summary, the available clinical data suggest that a subset of patients with cholangiocarcinoma may benefit from therapies blocking the PD-1 pathway. MEK inhibitors have also shown evidence of activity in cholangiocarcinoma and may synergize with immune checkpoint inhibitor therapy, supporting a combinatorial approach to the development of these therapies in cholangiocarcinoma.

2.4 Correlative Studies Background

A series of correlative studies are proposed to examine the impact of MEK inhibition with cobimetinib on biomarkers within the tumor microenvironment and systemically. Our primary objective will be to compare infiltration of CD8+ T cells into the tumor microenvironment between patients receiving atezolizumab alone and those receiving atezolizumab in combination with cobimetinib. This metric will be considered an integrated biomarker for the clinical study. The rationale for this is based on pre-clinical studies demonstrating the MEK inhibition can enhance T cell infiltration into tumors in murine models, limit their apoptosis and subsequently enhance the efficacy of immune checkpoint blockade. 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.

In addition to this integrated biomarker, we will assess a number of exploratory biomarkers in the context of correlative laboratory studies. These are based on the rationale that (1) patients with greater PD-L1 expression or antigen presenting capacity (as measured by MHC expression) will have a better response to immunotherapy; (2) MEK inhibitors may reverse exhaustive T cell death by reducing MEK-mediated phosphorylation of Nur77; and (3) Peripheral blood levels of immune suppressive T regulatory or myeloid derived suppressor cells may impact the response

to regimens containing atezolizumab. Based on these observations we also propose a series of correlative studies that will help us better understand the mechanism(s) underlying MEK's role in modulating tumor immunity, and to identify biomarkers that may predict response to therapy in the context of this clinical trial.

3. PATIENT SELECTION

3.1 Eligibility Criteria

All answers must be 'Yes' to eligible.

3.1.1 Pathologically confirmed metastatic or unresectable cholangiocarcinoma or gallbladder carcinoma (GBC), having received at least 1 prior line of systemic therapy, and received no more than 2 prior lines of therapy in the metastatic setting (disease recurrence ≤ 6 months from the last dose of adjuvant therapy in resected patients will be considered the first line of therapy).

- Includes intrahepatic cholangiocarcinoma (IHC), extrahepatic cholangiocarcinoma (EHC), and gallbladder carcinoma (GBC), but not Ampulla of Vater cancers.

3.1.2 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) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease. Assessment must be completed within 4 weeks of Randomization.

3.1.3 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of cobimetinib in combination with atezolizumab in patients < 18 years of age, children are excluded from this study.

3.1.4 ECOG performance status ≤ 1 (Karnofsky ≥ 80%, see Appendix A)

3.1.5 Life expectancy of greater than 2 months.

3.1.6 Patients must have normal organ and marrow function as defined below within 2 weeks of Randomization:

– leukocytes	≥ 2,500/mcL
– absolute neutrophil count	≥ 1,500/mcL
– platelets	≥ 75,000/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
– creatinine clearance	≥ 30 mL/min/1.73 m^2 by Cockcroft-Gault: $\frac{(140-\text{age})\times(\text{weight in kg})\times(0.85 \text{ if female})}{72\times(\text{serum creatinine in mg/dL})}$

OR

	Creatinine < 1.5 x ULN
– 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.)

3.1.7 Administration of atezolizumab and cobimetininb may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of childbearing potential must agree to use either two adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity (complete 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. Male patients must agree to use an adequate method of contraception, or to abstain from heterosexual activity (complete abstinence), prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of study agent.

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

3.1.9 Patients positive for human immunodeficiency virus (HIV) are allowed on study, but HIV-positive patients must have:

a. A stable regimen of highly active anti-retroviral therapy (HAART)
b. No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
c. A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests

3.1.10 Oxygen saturation ≥ 92% on room air

3.2 Exclusion Criteria

All answers must be 'No' to be eligible.

3.2.1 Received chemotherapy or radiotherapy within 3 weeks prior to Randomization or those who have not recovered to ≤ grade 1 adverse events (other than alopecia) due to agents administered more than 3 weeks earlier. Herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to randomization. For patients who received prior immunotherapy (eg anti-CTLA-4), at least five drug half-lives must have passed before the patient may enroll on this study. However, the following therapies are allowed:

- Hormone-replacement therapy or oral contraceptives.
- Palliative radiotherapy for bone metastases ≥ 2 weeks prior to randomization.

3.2.2 Prior treatment with a MEK inhibitor or ERK inhibitor.

3.2.3 Prior treatment with any anti-PD-1 or anti-PD-L1 antibody, prior allogeneic bone marrow

transplantation, or prior solid organ transplantation.

3.2.4 Treatment with any investigational agent within 4 weeks prior to Cycle 1, Day 1, or five drug half-lives (whichever is longer).

3.2.5 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 6 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.

3.2.6 Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases, with the following exceptions:

- Patients with <u>asymptomatic treated CNS metastases</u> may be enrolled, provided <u>all the criteria listed above are met as well as the following</u>:
  - Radiographic demonstration of clinical stability 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 randomization.
  - Screening CNS radiographic study ≥ 4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids.

3.2.7 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.

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

3.2.9 Allergy or hypersensitivity to components of the cobimetinib formulations.

3.2.10 History of congenital long QT syndrome or corrected QT interval (QTc) > 450 msec within 2 weeks of Randomization.

3.2.11 LVEF below institutional LLN or below 50%, whichever is lower, as determined by echocardiogram or MUGA scan within 4 weeks of randomization.

3.2.12 Patients who meet any of the following exclusion criteria related to ocular disease will be excluded from study entry:

- Known risk factors for ocular toxicity, consisting of any of the following:

– History of serous retinopathy
– History of retinal vein occlusion (RVO)
– Evidence of ongoing serous retinopathy or RVO at screening

3.2.13 Patients receiving any medications or substances that are strong 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). Such substances can significantly increase or decrease the serum level of cobimetinib. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as 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.

3.2.14 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.

3.2.15 History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

- 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:
  - 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).

3.2.16 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.

3.2.17 Severe infections within 4 weeks prior to randomization, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.2.18 Signs or symptoms of infection within 2 weeks prior to randomization.

3.2.19 Received oral or intravenous (IV) antibiotics within 2 weeks prior to randomization. Patients receiving prophylactic antibiotics (*e.g.*, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

3.2.20 Major surgical procedure within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study.

3.2.21 Administration of a live, attenuated vaccine within 4 weeks before randomization 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.

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

- Symptomatic CHF is defined as New York Heart Association (NYHA) CHF Class II or higher disease.

3.2.23 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.

3.2.24 Inability or unwillingness to swallow pills

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

3.2.26 Clinically significant ascites, defined as ascites that is symptomatic or has resulted in a paracentesis in the past 3 months

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.

DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1			2
Asian	3	4			7
Native Hawaiian or Other Pacific Islander					
Black or African American	5	6			11
White	23	27	5	5	60
More Than One Race	1	1			2
Total	33	39	5	5	82

3.4 Stratification factors

Eligible subjects will be stratified according to the site of disease: 1) gallbladder cancer (GBC); 2) intrahepatic (IHC); or 3) extrahepatic cholangiocarcinoma (EHC). There will be no further stratification based on other patient or tumor characteristics (such as age, sex) in this trial.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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.

Additional information can be found on the CTEP website at https://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 protocol #10139* 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 protocol NCI protocol #10139.
- 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 protocol #10139 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 must be completed and signed by site Study PI and sent back to the Protocol Liaison of the lead LAO.

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.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

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 or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- 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 Patient Enrollment Instructions

In order to verify eligibility, the following documents should be submitted to the Protocol Liaison of the Lead Organization at least 48 hours prior to treatment initiation:

- Completed Request for Registration form, along with requested supporting documents
- Signed consent form
- Signed eligibility checklist

After approval by the Lead Organization, the patient may be enrolled in OPEN.

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.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.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

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.

Arm A 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.	840 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.	Days 1, 15	28 days (4 weeks)

Arm B Regimen Description

Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Atezolizumab	Premeds are not permitted for the first infusion. If patient experienced an Infustion-Related Reaction (IRR) during any previous infusion, pre-medication with antihistamines may be administered for Cycles ≥ 2 at the discretion of the treating physician.	840 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.	Days 1, 15	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	PO once daily in the a.m.	Days 1−21	

NOTE: For patients receiving cobimetinib, the cobimetinib may be taken before or after the scheduled dose of atezolizumab on the days when both are to be administered (i.e., the drugs do not need to be sequenced in any particular order).

For patients receiving cobimetinib, patient will be requested to maintain a medication diary (see Appendix E) of each dose of medication. 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 and therefore administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before the infusion, every 15 [±5] minutes during the infusion, and 30 (±10) minutes after the infusion.

For subsequent infusions, vital signs will be collected within 60 minutes before and

within 30 minutes after the infusion. Vital signs should be collected during the infusion if clinically indicated.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (*e.g.*, acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. The management of Infusion Related Reactions will be according to severity as follows:

- In the event that a patient experiences a Grade 1 Infusion Related Reaction during Cycle 1, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.

- In the event that a patient experiences a Grade 2 Infusion Related Reaction, or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the Infusion Related Reaction. For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for Infusion Related Reactions.

- For Grade 3 or 4 Infusion Related Reactions, the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated (*e.g.*, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Atezolizumab should be permanently discontinued. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event; retreatment requires consultation with, and consent of, the trial Principal Investigator (PI).

For anaphylaxis precautions, use the following procedure: In event of an anaphylactic reaction, follow institutional procedures.

5.1.2 Cobimetinib

Patients randomized to cobimetinib will receive 60 mg (three tablets of 20 mg each) orally once daily in the morning for Days 1−21 of a 28-day cycle. This 4-week period is considered a treatment cycle. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.

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.

For patients receiving cobimetinib, the patient will be requested to maintain a medication diary (see Appendix E) 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 (Study Arms A and B)**

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 (except for maintenance therapies outlined in **Section 5.2.1**).
    - 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 for patients with solid malignancies.

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 (Study Arm B Only)**

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.

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 not meeting criteria dosing of study treatment beyond disease progression (see 5.3.1).
- 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.

5.3.1 Dosing of Study Treatment Beyond Disease Progression

Study treatment beyond disease progression on an imaging scan is allowed for patients on both treatment arms. However, participants who meet criteria for continued treatment must discontinue treatment upon documentation of disease progression on the second scan (relative to the scan that initially showed progression). Patients must also meet all of the following criteria to receive study treatment beyond disease progression:

- Evidence of clinical benefit as assessed by the investigator.
- Absence of symptoms and signs indicating unequivocal progression of disease.
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that are life threatening and cannot be managed by protocol−allowed medical interventions.
- No evidence of clinical deterioration and no evidence of progressive disease at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical

intervention.

- Patients treated beyond progression should receive their next follow-up scan 6-8 weeks following the initial assessment of radiological progression.

5.4 Duration of Follow Up

All subjects should continue to be monitored for disease status at least every three months until death, withdrawal of consent, or study closure, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from study at the time of death, withdrawal of consent, or study closure, whichever comes first.

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 or for a total of 112 days) 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 for up to 84 days. The appropriate length of interruption will be at the discretion of the study PI in consultation with CTEP. Patients receiving surgery or other procedures for unequivocal progression of disease (for example, malignant bowel obstruction) must be permanently removed from study treatment.

Atezolizumab must be **permanently discontinued** if the patient experiences any of the following events, regardless of benefit:

- Grade 4 pneumonitis
- AST or ALT > 5×ULN or total bilirubin > 3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Grade 4 ocular inflammatory toxicity
- Grade 4 pancreatitis or any grade of recurrent pancreatitis
- Grade 4 rash
- Any grade myocarditis

Treatment may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, <u>but only after consultation with the Study Principal Investigator</u>:

- Grade 3 pneumonitis
- Grade 3 ocular inflammatory toxicity
- Grade 3 or 4 infusion-related reactions

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo *et al*., 2010). Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab.

For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Investigator's Brochure and the FDA product label.

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.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

Systemic Immune Activation

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

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

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

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 **Section 5.1.1** for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

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.

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.

Endocrine disorders

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including 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 obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related 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.

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.

The table below presents management and dose modification guidelines for specific AEs. For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- Corticosteroids must be tapered to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Atezolizumab may be held for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
Abdominal pain	Acute abdominal pain	Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for "Amylase and/or lipase increase" and "Immune-related pancreatitis" elsewhere in this table, as needed. Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity (see the "Hepatotoxicity" guideline elsewhere in this table).

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
Adrenal insufficiency	Grade 2+ (symptomatic)	Hold atezolizumab. Refer patient to endocrinologist. Perform appropriate imaging. 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 and patient is stable on replacement therapy (if required) 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 or patient is not stable on replacement therapy within 12 weeks.
Amylase and/or lipase increased	Grade 1	Continue atezolizumab. Monitor amylase and lipase prior to dosing.
	Grade 2	Continue atezolizumab. Monitor amylase and lipase weekly. For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
	Grade 3	Hold atezolizumab. 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

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab.
Dermatologic toxicity/rash (*e.g.*, maculopapular or purpura)	Grade 1	Continue atezolizumab. Initiate symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2	Continue atezolizumab. Consider consultation with a dermatologist. Administer topical steroids. Consider higher potency topical steroids if rash does not improve.
	Grade 3	Hold atezolizumab. 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.
	Grade 4	Permanently discontinue treatment. 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.
Diarrhea or	Any grade	Patients should be advised to inform the

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
colitis		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. 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. 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.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		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 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. 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 resume atezolizumab 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

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		from the immune-related event.
	Grade 4	Permanently discontinue atezolizumab. 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. 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.
Hepatotoxicity	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. Monitor LFTs until values resolve to within normal limits.
	Grade 2 hepatic event, ≤5 days	Continue atezolizumab. Monitor LFTs more frequently until values resolve to baseline values.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
	Grade 2 hepatic event, >5 days	Hold atezolizumab. 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 according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks.
	Grade 3 or 4 hepatic event	Permanently discontinue atezolizumab. 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.
Hyperglycemia	Grade 1 or 2	Continue atezolizumab. Initiate treatment with insulin if needed. Monitor for glucose control.
	Grade 3 or 4	Hold atezolizumab. Initiate treatment with insulin. Monitor for glucose control. Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperthyroidism	Grade 1 (asymptomatic)	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** Continue atezolizumab. Monitor TSH every 4 weeks.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		TSH < 0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism.
	Grade 2+ (symptomatic)	Hold 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 for life-threatening immune-related hyperthyroidism.
Hypothyroidism	Grade 1 (asymptomatic)	Continue atezolizumab. Start thyroid-replacement hormone. Monitor TSH weekly.
	Grades 2+ (symptomatic)	Hold atezolizumab. Start thyroid-replacement hormone. Consider referral to an endocrinologist. Monitor TSH weekly. Restart atezolizumab when symptoms are controlled and thyroid function is improving.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
Meningo-encephalitis, immune-related (signs and symptoms in absence of an identified alternate etiology)	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Myasthenia gravis and Guillain-Barré syndrome	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.
Myocarditis	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.
Myositis	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.
Neuropathy, immune-related (sensory and/or motor)	Grade 1	Continue atezolizumab. Evaluate for alternative etiologies.
	Grade 2	Hold atezolizumab. Evaluate for alternative etiologies. Initiate treatment as per institutional guidelines. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.
	Grade 3 or 4	Permanently discontinue atezolizumab. Initiate treatment as per institutional guidelines.
Ocular event (*e.g.*, uveitis, retinal events)	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 for more than 1 week, treat as a grade 2 event.
	Grade 2	Hold atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to grade 1 or better 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.
	Grade 3 or 4	Permanently discontinue atezolizumab. Refer patient to ophthalmologist. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment after

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.
Pancreatitis, immune-related	Grade 2 or 3	Hold atezolizumab if radiologic findings or physical exam findings are suggestive of immune-related pancreatitis. Note: If amylase/lipase ≥ 2X ULN, refer to GI specialist and consider scan to evaluate for immune-mediated pancreatitis. Refer patient to GI specialist. 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 resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. Patient may only resume treatment after consultation with the trial PI. For recurrent events, permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist. 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 does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Pulmonary toxicity	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 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. 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 according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, treat as a Grade 3 or 4

AE Management and Dose Interruption Guidelines for Specific Toxicities in Treatment		
Toxicity	**Severity/ Duration**	**Management**
		event.
	Grade 3 or 4	Hold atezolizumab. 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.

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 6.3. The following general dose modifications table for cobimetinib is for AEs not specified in the subsequent tables.

Grade (CTCAE)[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

6.3 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
Hepatoxicity has been associated with the administration of atezolizumab and cobimetinib. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment.

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

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

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 (e.g., maculo-papular or purpura)	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.

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.
Grade 4	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.

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 have 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 2 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 more than 10% 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 resolved, 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 ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). 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 ECG, 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 ECG, 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.

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 List(s) (CAEPRs)

The Comprehensive Adverse Event 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 of AEs, 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 Agent(s)

7.1.1.1 CAEPR for Atezolizumab

Below is the CAEPR for Atezolizumab. Frequency is provided based on 1369 patients.

Version 2.1, June 7, 2017[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 4.0 Term) [n= 1369]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	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 4.0 Term) [n= 1369]			**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 (hypophysitis)[2]	
	Hyperthyroidism[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]		
	Infusion related reaction[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFECTATIONS			
		Meningitis[2]	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 4.0 Term) [n= 1369]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
	GGT increased[2]		
	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]		
		Generalized muscle weakness	
	Myalgia[2]		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (Guillain-Barre syndrome)[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Nervous system disorders - Other (myasthenia gravis)[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 4.0 Term) [n= 1369]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
	Skin and subcutaneous tissue disorders - Other (lichen planus)[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.

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:

Cardiac disorders - Cardiac arrest
Gastrointestinal disorders - Constipation; Ileus
General disorders and administration site conditions - Chills; Edema limbs; Malaise; Pain
Infections and infestations - Lung infection; Sepsis; Urinary tract infection
Investigations - Weight loss; White blood cell decreased
Metabolism and nutrition disorders - Hypophosphatemia; Tumor lysis syndrome
Musculoskeletal and connective tissue disorders - Back pain; Bone pain

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
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).

Version 2.0, April 19, 2017[1]

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 4.0 Term) [n= 115]			**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			
		Heart failure	
EYE DISORDERS			
	Blurred vision		
	Eye disorders - Other (chorioretinopathy)[2]		
		Eye disorders - Other (retinal vein occlusion)[2]	
	Eye disorders - Other (visual impairment)		
	Retinal detachment		
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (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)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INVESTIGATIONS			

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 4.0 Term) [n= 115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	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)***
	GGT increased[2]		***GGT increased[2] (Gr 2)***
	Investigations - Other (left ventricular ejection fraction decreased)		
METABOLISM AND NUTRITION DISORDERS			
Dehydration			***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Photosensitivity[2]		***Photosensitivity[2] (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Hypertension		
	Vascular disorders - Other (hemorrhage)[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]Observed in combination with Vemurafenib.

[3]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:

NERVOUS SYSTEM DISORDERS - Headache
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (hyperkeratosis)

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.

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** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event 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 SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events 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 notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE 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: May 5, 2011

7.3.4 Adverse Events of Special Interest

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). Adverse events of special interest for this study include the following:

- Pneumonitis [atezolizumab]
- Colitis [atezolizumab]
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism or hypophysitis [atezolizumab]
- Systemic lupus erythematosus [atezolizumab]
- Neurologic: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis [atezolizumab]

- Nephritis [atezolizumab]
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation [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., uveitis, retinitis) [atezolizumab]
- Significant muscular toxicities
    - Rhabdomyolysis or Grade ≥ 3 CPK elevation [cobimetinib]
    - Myopathies including myositis [atezolizumab]
    - Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage [cobimetinib]
    - Grade ≥ 3 rash [cobimetinib and atezolizumab]
- Grade ≥ 2 cardiac events including:
    - Symptomatic heart failure or Grade ≥ 3 left ventricular ejection fraction reduction [cobimetinib]
    - Myocarditis, pericarditis, or atrial fibrillation [atezolizumab]
- Vasculitis [atezolizumab]
- Significant liver toxicity [concern for cobimetinib and atezolizumab]
    - Hepatitis, including AST and/or ALT > 10 ×ULN
    - 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 either an elevated total bilirubin (> 2× ULN) or clinical jaundice, without initial findings of cholestasis (elevated serum alkaline phosphatase)
        - No other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as: liver metastasis; viral hepatitis A, B, or C; alcoholic and autoimmune hepatitis; other liver diseases; or exposure to other drugs known to cause liver injury
- Suspected transmission of an infectious agent by the study drug, 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 the study drug is suspected.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> 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 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.

7.6 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 agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

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. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at 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 250 mL 0.9% NaCl and infused through a 0.2 micrometer in-line filter. The IV bag may be constructed of PVC or PO; the IV infusion line may be constructed of PVC or PE; and the 0.2 micrometer in-line filter may be constructed of PES. The prepared solution may be stored at 2°C-8°C or room temperature for up to 8 hours.

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 antihistamines or antipyretics/analgesics (e.g. acetaminophen) for 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 5 months (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.

8.1.3.3 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
- 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)
- IB Coordinator: IBCoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Hypotheses and background

A series of correlative studies are proposed to examine the impact of MEK inhibition with cobimetinib on the tumor microenvironment and systemically. Our primary objective will be to compare infiltration of CD8+ T cells into the tumor microenvironment between patients receiving atezolizumab alone and those receiving atezolizumab in combination with cobimetinib. This metric will be considered an integrated biomarker for the clinical study. The rationale for this is based on pre-clinical studies demonstrating the MEK inhibition can enhance T cell infiltration into tumors in murine models, limit their apoptosis and subsequently enhance the efficacy of immune checkpoint blockade. 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.

In addition to this integrated biomarker, we will assess a number of exploratory biomarkers in the context of correlative laboratory studies to better define the impact of these agents on the TME. These are based on the rationale that (1) patients with greater PD-L1 expression or antigen presenting capacity (as measured by MHC expression) will have a better response to immunotherapy; (2) MEK inhibitors may reverse exhaustive T cell death by reducing MEK-mediated phosphorylation of Nur77; and (3) Peripheral blood levels of immune suppressive T regulatory or myeloid derived suppressor cells may impact the response to regimens containing atezolizumab. Based on these observations we propose a series of studies to address the hypothesis that these factors may serve as biomarkers to predict response to therapy in the context of this clinical trial.

This clinical trial is a 2-arm randomized Phase II study that will incorporate a series of both intratumoral biomarkers that can be assessed from patient biopsy materials as well as those within the peripheral blood. The randomized nature of this trial has a number of inherent advantages whereby the contribution of MEK inhibitor on immune modulation can be accurately compared to a relevant control arm in which patients receive atezolizumab alone.

9.2 Preliminary data

It has been demonstrated in other malignancies that the presence of CD8+ effector T cells within tumors increases the likelihood of responding to PD-1/PD-L1 antibody blockade. Pre-clinical studies demonstrate that the inclusion of a MEK inhibitor may enhance the access of these T cells to the tumors, while concurrently promoting their survival (Ebert et al. 2016). Together these data justify the choice of CD8+ T cells as an integrated biomarker that should be assessed in the context of this clinical study. This assay is conducted routinely on FFPE tissue in our clinical pathology laboratory, from which we have implemented the protocol with additional biologic and quality controls for the purpose of this study.

We propose a series of correlative studies that will be used concurrently to identify other potential biomarkers that deserve further investigation in future studies.

Depending on the quantity of tissue obtained from each patient enrolled in this study, we estimate that a portion of FFPE or frozen blocks sufficient for another 8-10 slides cut at 3-4 µM will be remaining. In addition, it is likely that an additional cryopreserved vial of peripheral blood mononuclear cells (~3 x 10^6 total) and 3 – 5 mL of patient plasma will remain following our immune phenotyping studies. In previous studies with paired core biopsies we have obtained an average of 3-4 cores per patient.

9.3 Methods

9.3.1 Archival Tumor Tissues

Attempts to obtain biopsy or surgical archival tumor samples will be made for every subject. The tissue sample should have proper size to enable analysis. Request for tissue samples should begin during Screening Visit and continue to be requested until tissue sample is obtained or documentation that the sample cannot be obtained. Samples should be from the most recent biopsy or surgical resection of the original tumor (or metastatic site, if original tumor is not available).

One formalin-fixed paraffin-embedded tissue block, or cut unstained slides will be requested. If sufficient tissue is available, we request 1 H&E cut at 4 micrometers, 30 unstained sections, cut at 4 micrometers and mounted in poly-l-lysine-coated or plus (+) slides, and 30 sections containing at least 50% tumor cut at 10 micrometers and mounted on glass slides. If the tissue is small (< 1cm^2), then 12 unstained sections cut at 4 micrometers of thickness are requested. These latter slides will be air dried (not oven-dried). The slides will be stored at room temperature (>16°C).

The sectioning of FFPE tissue for the immunohistochemical studies, and molecular study should be done at the same time as the standard clinical H&E section and the immunohistochemical sections to minimize tissue loss. Remaining tissue will be archived by the Pathology Department at each respective institution. FNA samples do not contain adequate material for analysis and will not be requested.

The following guidelines should be used for preparation of slides:

- Slides #1: to be regular 4 microns, positively charged slide, H&E, with cover
- Slides #2 and above: 4 microns, positively charged slides, unstained, NO COVER
- Blades need to be changed between blocks, if more than one block is being cut.
- If possible, slides and process need to be DNAase free and tissue should be mounted on the bottom third of the slide.

9.3.2 Fresh Tumor Specimens

9.3.2.1 Collection of Specimens

Supplies
- 10% Neutral Buffered Formalin (ambient/room temperature) (VWR #16004-115)
- RNA*later*™ (refrigerated at 4ºC for ≥16 hours *prior* to biopsy procedure)
- Cryovial tubes – 1.8 ml cryotubes/vials (e.g., Nunc Code #377267 or equivalent)
- Conical tubes – 15 mL (e.g., Sarstedt Code #62.554.001 PP or equivalent)

For patients with tumor that is amenable to biopsy, core biopsies will be collected at study baseline and at cycle 1 day 21 (+/-5 days). A maximum of 6 core biopsies (<u>or fine needle aspirates, if cores are considered unsafe</u>) will be obtained from each subject whose tumor is amenable to undergo a biopsy. The biopsies will be used to prepare paraffin embedded and frozen samples. A total of 6 biopsies is preferred, when possible. The first pass will generally be used for on-site examination of the material, to determine presence and quality of lesional tissue. The remaining biopsy tissue will be paraffin embedded and frozen at each respective institution. If a limited amount of tumor tissue is obtained, paraffin embedded tissue should be prioritized over frozen tissue. Archived or freshly obtained paraffin embedded formalin fixed (FFPE) or frozen tissues of biopsied specimens are needed for the purposes of:
- Pathological examination (for conventional pathology examination, such as H&E stain)
- Examination of immune and inflammatory fibroblast biomarkers via IHC or IF analysis, as appropriate.
- Future analysis of genomic and transcriptome features within the tumor microenvironment.

<u>Samples will be collected in this order:</u>
Core 1 – Formalin-fixed paraffin-embedded (FFPE)
Core 2 – FFPE
Core 3 – Snap Frozen
Core 4 – FFPE
Core 5 – FFPE
Core 6 – Frozen in RNA*later*™

For example, if only 2 cores are obtained, both should be set aside and preserved for IHC analysis (FFPE). If 5 cores are obtained, four should be set aside and preserved for IHC analysis and one core should be snap frozen.

9.3.2.2 RNA*later*™ samples
- The cryovial containing a single core biopsy in RNAlaterTM must be placed back in the refrigerator (4ºC) for ≥16-24 hours after the biopsy procedure.
- After ≥16-72 hours at 4ºC, the RNAlaterTM samples/vials must be transferred to -80ºC or below for storage.
- Frozen samples should never be thawed until RNA isolation.

9.3.2.3 Shipping of Tumor Specimens

- Tissue samples (archival and fresh tumor biopsies) should be shipped to JHU biannually. Tissues for correlative research studies will be shipped from each institution to Dr. Nilo Azad at Johns Hopkins University, for analysis of integrated

(CD8+, PD-L1 staining) and exploratory biomarkers outlined below. Please call ahead or email (nazad2@jhmi.edu, mark.yarchoan@jhmi.edu, and ssolt1@jhmi.edu) to alert us of shipment with tracking number if available. To ensure the integrity of tissue specimens, shipment should occur on Monday-Wednesday to avoid unanticipated delivery delay due to weekends or holidays.

- Frozen tissue samples must be shipped frozen and maintained in the frozen state. All shipments should be made in freezer boxes containing DRY ICE, and labeled as HUMAN SAMPLES: NONINFECTIOUS.

- Each tumor sample must be clearly labelled with the study number (10139), the subject's ID, the date and time of collection, tissue biopsy site (i.e. liver), the study time point (i.e. BL, C1D21), and the tissue type (i.e. frozen RNA Later)

The shipping address for **Tissue Samples** (NOT RESEARCH BLOODS) is as follows:

Sara Solt
Attn: NCI 10139
1550 Orleans Street
CRBI Room 422
Baltimore, MD 21287

3. Immunohistochemical analysis of tumor tissue

Paired tumor biopsies will be used to assess the effect of treatment arm on changes in the TME. This analysis will be performed on paired samples from patients enrolled in the trial. Baseline pretreatment biopsies, when available, will be collected. In addition, specimens from the on-treatment biopsy will be collected under the guidance of the collaborating pathologist and tissue procurement staff at the time of biopsy.

Our study design will enable us to isolate the effect of each treatment arm treatment combinations on immune cells, and other biomarkers in the TME in the context of atezolizumab +/- cobimetinib. For the integrated biomarker of CD8+ staining, IHC assays will be conducted in a Central Reference CLIA Laboratory using the Cell Marque, CD8 (C8/144B), mouse monoclonal antibody, Ref#108M-98, Status IVD. Further technical details for this biomarker are listed in appendix C. PD-L1 expression will be another integrated biomarker and will be conducted in a Reference CLIA Laboratory.

In addition to these integrated biomarkers, a series of exploratory biomarkers will be assessed on tissue from this study. A sample of immune and other markers in **Table 1** will be the stains of high priority for these exploratory investigations, in order of priority based on amount and quality of tissue obtained. In addition to this panel, we will explore the impact of cobimetinib on a subset of $CD8^+$ T cells identified by Dr. Rafi Ahmed (Emory University) ($CD8^+Ki67^+$) that displays a proliferative burst after PD-1 blockade and may be a potential biomarker of response to anti-PD-1 therapy (Kamphorst et al. 2017). This panel can also be expanded for other co-stimulatory or immune checkpoint molecules on cell subsets (i.e. CD8, Tim3, LAG3) (Tsujikawa et al. 2017).

Briefly, we will utilize a validated quantitative multiplex immunohistochemical platform co-developed at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and the Knight Cancer Institute at Oregon Health and Science University that has previously been used to characterize the tumor microenvironment. This technology incorporates a computational image processing workflow, including image cytometry, that enables simultaneous evaluation of 12 biomarkers in one formalin fixed paraffin-embedded tissue section. This platform is readily adaptable to assess a variety of markers including lymphoid and myeloid lineage markers, in addition to those listed below (Tsujikawa et al. 2017).

Table I. Planned Immunohistochemical (IHC) and Immunofluorescence (IF) analysis (*denotes integrated biomarker)

IHC Stains	IF Stains	
CD8* PD-L1* CD4	CD8+Ki67+ CD8+Nur77+	**Priority 1**
CD11c CD19 CD68 CD163 CTLA4 PD1 PD-L2 IDO1 LAG3 pERK ERK	CD4+FoxP3+ CD33+S100+ CD4+IL-17+	**Priority 2**

4. Analysis of IHC/IF data

After staining, slides will be analyzed in the Cell Imaging Core Facility at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center to quantitate the percentage and intensity of cells for each marker(s) in the TME.

For analysis of CD8+ cells as an integrated biomarker, the specific image measurement/ analysis strategy is described in the appendix.

The exploratory biomarker data will be captured for samples according to a digital image workflow. Briefly, this encompasses three steps: image preprocessing, visualization, and quantitative image analysis using state-of-the-art software in the Core Lab. This system allows for true quantitative data on dual staining in patient samples. These IHC and IF analyses will be conducted under the guidance of Dr. Robert Anders. To ensure the rigor of these analyses, samples will be batch run when possible, with appropriate positive (i.e. tonsil tissue for immunostains) and negative controls (secondary Ab only) along with serial sections from a single archival cholangiocarcinoma tumor specimen as a qualitative control to for intensity and any batch-to-batch variability between reagents used in IHC or IF assays.

5. Excess tumor tissue
When sufficient quantity permits, a section of fresh tumor biopsy samples will be split and snap frozen in liquid nitrogen either (1) alone for future genomic analysis or (2) in RNALater solution to facilitate future high throughput analysis of gene expression profile. Samples will be stored immediately in cryovials at -80°C for future analysis.

9.3.3 Blood Specimens

9.3.3.1. Specimen Collection
Blood samples will be collected prior to dosing of both study drugs at baseline (day 1), prior to dosing on cycle 1 day 15, prior to dosing on cycle 2 day 1, and at the time of progression. Three 10 mL purple top tubes of blood containing EDTA as an anti-coagulant will be obtained for correlative studies at each of these time points.

Adherent labels will be placed on each tube and using an ethanol-resistant permanent marker write the following information: the study number (10139), the subject's ID, the date and time of collection, and the study time point (i.e. BL, C1D15, or PD)

9.3.3.2. Specimen Shipping
Samples should be shipped the same day as collection and can be stored at ambient temperature until shipped. To ensure quality of the cells and plasma, it is imperative that samples be shipped on Monday – Thursday only to avoid problems with weekend/holiday delivery. For shipment of blood samples, specimens will remain in the purple top tubes, which are to be placed into a cardboard box containing Styrofoam holders that stabilize the glass tubes. An ice pack should be added to each shipment to reduce temperature for shipment. The box containing blood and cold pack should be contained within a Fed-Ex UN3373 Clinical Pak. All blood specimens should be shipped via Fed-Ex priority overnight the same day of collection for next day processing and analysis to the address below.

The shipping address for **Research Bloods** (NOT TUMOR BIOPSIES) is as follows:

Lesinski Laboratory
Suite C3038, Bay 34
1365-C Clifton Rd. NE
Winship Cancer Institute of Emory University
Atlanta, GA 30322

On the day that the specimens are to be shipped, notify Dr. Matthew Farren at matthew.r.farren@emory.edu, and Dr. Gregory Lesinski at gregory.b.lesinski@emory.edu of the pending specimen shipments. Include the Fed-Ex tracking number in the email.

Contact Information:
Matthew Farren, Ph.D. 404-778-8230
Gregory B. Lesinski, Ph.D., MPH 404-778-3072

9.3.2.4 Specimen Processing

Specimens will be processed at the central site (Lesinski Laboratory, Winship Cancer Institute of Emory University). Blood samples will be centrifuged at room temperature at 805 x *g* for 10 minutes and the plasma layer will be aspirated with a sterile pipet, aliquoted, snap frozen (dry ice or liquid nitrogen) and stored at ≤-70°C until analysis. Plasma samples from individual patient cohorts will be batched and analyzed simultaneously.
Peripheral blood mononuclear cells will be isolated from these same blood samples following removal of the plasma layer. This will be accomplished via standard methods using density gradient centrifugation with ficoll-paque plus as described (Farren et al. 2016). Following isolation PBMCs will be resuspended in PBS, counted via trypan blue exclusion and aliquoted into tubes for phenotypic and functional analysis via flow cytometry staining (see detailed methods below). PBMCs in excess of what is needed will be pelleted, resuspended in cell freezing media, aliquoted into cryovials and placed into Nalgene Mr. Frosty containers for overnight storage at -80°C. The following day the samples will be placed into long-term storage in the vapor phase of liquid nitrogen.

9.3.2.5 Phenotypic analysis of immunomodulatory cytokines and immune suppressor cell populations

Elevated levels of pro-inflammatory cytokines and immunosuppressive cell populations are present in patients with cancer. Our group has previously conducted pilot studies and demonstrated that this profile is also operative in peripheral blood from patients with advanced gastrointestinal cancers. For example, plasma IL-6, IL-10 and MDSC were elevated in patients as compared to normal donors (Farren et al. 2016). Furthermore, in a cohort of n=73 treatment naïve patients with metastatic PDAC, plasma IL-6 and IL-10 were correlated with worse overall survival (Farren et al. 2016). These factors may reflect an altered cellular milieu present in the tumor microenvironment or systemically that favors reduced anti-tumor immune responses mediated by T lymphocytes.

9.3.2.6 Cytokine analyses:

Cytokines in patient plasma will be analyzed in samples obtained at baseline, day 15 and time of progression using a high-throughput bioplex analysis as described by our group (Farren et al. 2016). Our analysis will focus on a panel of n=32 cytokines and chemokines. These represent the following functional classes: 1) analytes shown by our group as expressed from cholangiocarcinoma cells; 2) cytokines/chemokines that are documented to promote MDSC or T regulatory cell expansion or migration; 3) cytokines involved in Th1/Th2/Th17 differentiation. All patient samples will be run in duplicate, and compared to pre-specified standard curves to obtain quantitative data. Duplicate samples displaying a CV>10% will be re-analyzed with additional replicates for greater accuracy. Given its relevance in both progression of gastrointestinal cancers, a separate aliquot of plasma will be utilized to assess expression of TGF-β via standard ELISA assay as this analyte is not compatible with the proposed bioplex analysis.

9.3.2.7 Immune suppressor cell analyses

The expansion of immune suppressive cytokines and particular cell populations represent

important barriers that likely limit the full potential of immune-based therapies or endogenous host responses to tumors. We hypothesize that this state of elevated immune suppressor cells in cancer patients can be manipulated via MEK inhibition to provide an advantage for the maximal therapeutic effect of immune checkpoint blockade. For these experiments, multiparameter flow cytometry will be utilized to phenotype immune effector cells to determine whether cobimetinib containing regimens downregulate T regulatory cells (based on expression of CD4, CD25, CD127, CD49d and FoxP3), IL-10-producing B regulatory cells (based on expression of CD5, CD19, CD1d, CD24, CD25, CD27, CD38 and IL-10) and myeloid derived suppressor cells ($CD33^{+}HLADR^{-}CD11b^{+}$ plus $CD14^{+}$ or $CD15^{+}$) as these populations can neutralize host anti-tumor responses and could be modulated in response to cobimetinib. Namely, it is possible that cobimetinib could directly interact with these cells, or the ability of this agent to limit tumor growth, and indirectly reduce expansion of these cell populations. Briefly, these freshly procured cells will be aliquoted at $5 \times 10^5 – 1 \times 10^6$ cells/flow tube in PBS containing 5% FBS (flow buffer). Cells will be incubated at 4°C with the following fluorochrome conjugated Ab for 45 minutes. Cells will then be washed twice with 2 mL flow buffer and pelleted via centrifugation at 805 *x g* for 10 minutes. Following decanting of flow buffer from the final wash, cells will be resuspended in 300 uL 1% formalin and stored in the dark at 4°C. Samples will be analyzed on a BD LSR II flow cytometer in the Emory University School of Medicine Flow Cytometry Core Facility. All data will be expressed as the percentage of total circulating peripheral blood cells with each respective phenotype. Appropriate fluorochrome labeled isotype control antibodies will be utilized for determination of background staining and for compensation. The phenotypes chosen represent the most well-accepted and published phenotypic definitions to date, and will be modified as concordance among the tumor immunology community becomes more apparent.

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 Study[N]
		Day 1	Day 15	Day 21	Day 1	Day 15	
Visit window[A]	*-14 to -1*	*+/-2*	*+/-2*	*+/-5*	*+/-2*	*+/-2*	*+/-7*
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	X
Height	X						
Weight	X	X			X		X
Performance status	X	X			X		X
CBC w/diff[E]	X	X	X		X	X	X
Serum chemistry[E]	X	X	X		X	X	X
Coagulation (INR and aPTT)	X						
Thyroid function test[F]	X				X		
EKG	X						
B-HCG[G]	X						
CPK	X				X[O]		
ECHO or MUGA[H]	X[H]	1 month after first dose, then every 3 months on cobimetinib (see [H])					
Ophthalmologic exam[I]	X[I]	Every 2 months for 1 year, then every 6 months while on cobimetinib (see [I])					
Adverse event evaluation		X	X		X		X[P]
Tumor measurements[J]	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease if possible.					X[Q]
CEA and CA 19-9[E]	X	X			X		X
Archival tumor sample	X						
Tumor biopsy[K]	X			X			
Peripheral blood for research[L] (up to 50cc)		X[L]	X		X[L] (C2D1 Only)		X
Atezolizumab		X	X		X	X	
Cobimetinib[M]		[----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. CEA and/or CA19-9 do not need to be repeated in the event that the screening lab draw show that the patient's tumor does not secrete CEA and/or CA19-9.
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: Baseline evaluation of LV function by either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) will be performed for all participants < 4 weeks prior to randomization *(study arms A and B).* Repeat ECHO and MUGA 1 month after first dose

(visit window +/-7 days), then every 3 months (visit window +/-7 days), while on cobimetinib only *(study arm B only).*

I: Ophthalmologic examination will be performed for all participants < 4 weeks prior to randomization *(study arms A and B).* Repeat ophthalmologic examination will be performed every 2 months for 1 year, then every 6 months while on cobimetinib (visit window +/- 14 days); *(study arm B only)*. Eye exam should include retinal exam, slit lamp exam, and visual fields (preferably Humphrey Visual Field or Goldmann Visual Field, if available) for evidence of retinal pathology and other abnormalities. Patients with ocular symptoms occurring during study treatment should be examined by an opthamologist

J: Baseline scans must be done < 4 weeks prior to randomization. Tumor measurement will be performed with contrast CT chest/abdomen/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. Imaging will be repeated every 8 weeks (+/-4 days), irrespective of dosing schedule or treatment delays. For patients continuing treatment past progression, the subsequent scan should be performed 6-8 weeks following the initial scan demonstrating progression (see section 5.3.1.). If this repeat scan does not show further progression, imaging frequency can revert to every 8 weeks (+/-4 days).

K: Only for subjects with tumor that in the opinion of the study treatment team is safely accessible for biopsy.

L: Baseline research blood collection will be collected prior to dosing of any study therapy (visit window day -7 to 0, prior to dosing). Additional on-treatment research bloods will be collected on cycle 1 day 15 (day -4 to 0), on cycle 2 day 1 (day -4 to 0), and at the time of progression (+/-7 days). No research blood is needed for day 1 of any cycle beyond cycle 2. Research blood samples should be collected and shipped on Monday-Thursday only to avoid problems with weekend/holiday delivery. For additional details, see section 9.3.1.

M: For patients randomized to cobimetinib plus atezolizumab *(study arm B only)*.

N: Off-study evaluations will be completed 4 weeks after meeting at least one of the criteria listed in section 5.3.

O: Patients receiving cobimetinib *(study arm B only).*

P: Adverse events will be assessed at least 90 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.

Q: Scans do not need to be repeated if a scan has been performed within 8 weeks.

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.

This study will [also] evaluate response and progression using immune-related response criteria (irRC) (Wolchok *et al*., 2009). See **Appendix D** for a detailed description of the evaluation criteria.

11.1.1 Definitions

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

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	
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) or until death.

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, or until death.

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)

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

Note: For participants who receive treatment beyond disease progression (as described in 5.3.1), PFS will be dated as follows.

- For patients who have progressive disease on two sequential scans, the date of progression will be backdated to the time of first progression.
- For patients who do not have progressive disease on the scan after progressive disease was first documented, the date of progression will be dated to the time that a second scan shows progression.

11.1.7 Overall Survival (OS)

OS is defined as the duration of time from date of randomization 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 Study 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 Study Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

The Study Principal Investigator will have, at a minimum, quarterly conference calls with the site Investigators, study collaborators, and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance.

All Site Principal Investigators 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, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site 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 Protocol 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) 799-7580 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

- N/A

12.4 Collaborative Agreements Language

The agent(s) 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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The proposed study is an open-label, randomized phase 2 multicenter trial evaluating cobimetinib in combination with atezolizumab compared with atezolizumab monotherapy in unresectable cholangiocarcinoma.

The primary clinical endpoint is progression free survival and the primary objective of the trial is to determine whether the combination of cobimetinib in combination with atezolizumab yields a clinically compelling antitumor activity measured as progression free survival (PFS). Additional secondary endpoints include safety, objective response rate (ORR, assessed by RECIST 1.1), overall survival (OS), and other immunologic correlates.

The principle correlative objective of the trial is to determine whether the combination of cobimetinib and atezolizumab increases immune response compared to atezolizumab monotherapy. The change CD8+ density within tumor after 21 days of treatment, as compared to baseline, is an integrated biomarker for this clinical trial.

The study is planned with 76 evaluable subjects (38 subjects per treatment arm), to achieve 90% power using a 1-sided test with alpha=0.05. Both of these drugs are in common use and will be given at full dose. The combination of cobimetinib and atezolizumab was previously tested, and well tolerated in a similar population of patients with metastatic colorectal cancer, so unacceptable rates of toxicity are not expected, but the present study will be continuously monitored for adverse events. The primary study team made up of the study PI Dr. Azad, Lead Associate Investigator Dr. Yarchoan, and lead study nurse and coordinator at the lead site Johns Hopkins will meet weekly to discuss adverse events. In addition, the primary study team will have bimonthly calls with representatives at all the enrolling sites to monitor toxicity continuously.

Progression-free survival is defined as the duration of time from date of randomization to time of progression or death. The evaluable population includes all subjects who have completed at least one dose of therapy and have received at least one follow-up scan. Patients who come off of study treatment for clinical progression prior to the first follow-up scan (i.e. clinical progression)

will also be considered evaluable and will be coded as progressors for the analysis. Due to the rapid progression of the disease in the majority of patients, little loss to follow up is expected, but subjects who are lost to follow-up as of the data analysis cutoff date will be right-censored. The censoring date will be determined from the date the subject was last evaluated for progression. PFS within each treatment arm will be summarized descriptively using Kaplan-Meier plots, and compared between groups, under the assumption of Cox proportional hazards, using the stratified log-rank test to account for tumor site. An interim analysis will be conducted when half the required PFS events have been observed (35). The trial will be stopped early for futility if the p-value from the log-rank statistic is greater than 0.5 (i.e., the PFS is worse for study arm B than for study arm A).

The analysis will be stratified on site of disease (gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma). An interim analysis will be conducted when half the required PFS events have been seen (35), and the trial will be stopped early for futility if median PFS is lower by any amount, under the combination therapy than under monotherapy.

13.2 Sample Size/Accrual Rate

Approximately 82 patients with unresectable cholangiocarcinoma will be enrolled in this randomized phase 2 trial with the goal of accruing at least 76 evaluable subjects, with progression free survival (PFS) as the primary endpoint. We plan to enroll approximately 6 patients per month across the multiple trial sites, and because of the rapid progression of the disease, expect little or no censoring. We anticipate fully enrolling this trial within 18 months, permitting an average of 12 months of follow up, and completing the study within 3 years. This design yields 90% power at a one-sided type I error rate of 5% assuming a difference in median PFS between the arms of 2 months (2 months vs. 4 months), and assuming that 71 events will have occurred among 76 patients over the study period. Calculations were performed without stratification, as it is not known whether outcome varies by site.

Patients with tumor that is safely accessible for biopsy will obtain a biopsy at study baseline and a repeat on-treatment biopsy at treatment day 21. Based on previous clinical experience, we anticipate that paired biopsy samples will be successfully obtained in at least 50% of participants. We anticipate obtaining approximately 20 subjects in each treatment arm with paired samples available for analysis, offering 80% power for detecting an increase in CD8+ density equal to 0.8s.d., using a one-sided t-test with alpha=0.05, and more than 90% power for detecting an effect size of 1.0s.d.

13.3 Stratification Factors

After the screening phase, eligible subjects will be stratified according to the site of disease: 1) gallbladder cancer (GBC); 2) intrahepatic (IHC); and 3) extrahepatic cholangiocarcinoma (EHC). There will be no further stratification based on other patient or tumor characteristics (such as age, sex) in this trial. Sample size calculations were performed without stratification, as it is not known whether outcome varies by site.

13.4 Analysis of Secondary Endpoints

Overall survival is defined as the duration of time from date of randomization to time of death. Subjects lost to follow-up or whose vital status is unknown, will be right-censored at the date the subject was last known to be alive. Every effort will be made to determine outcome, including phone calls, certified mail, and the checking of public records as necessary. The evaluable population is as defined for the primary endpoint. Results will be summarized descriptively using Kaplan-Meier plots, and compared between groups, under the assumption of proportional hazards, using the stratified log-rank test to account for tumor site.

The density of CD8+ T cells in each treatment group, at baseline and after treatment, will be visualized using boxplots, and described using summary statistics including means and s.d. presented with 95% confidence intervals. A student t-test or nonparametric Wilcoxon rank-sum test will be used to determine whether the increase in CD8+ T cells is greater in treatment arm B (combination cobimetinib plus atezolizumab) than in treatment arm A (ateozolizumab monotherapy).

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 ECGs. 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, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

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, and an exact binomial test will be used to compare response rates across treatment groups.

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.

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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 HANDOUTS AND WALLET CARDS

PATIENTS ON STUDY ARM A (ATEZOLIZUMAB MONOTHERAPY)

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 drug atezolizumab (trade name Tecentriq). 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 (eg, 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.

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®) 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.

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 drug atezolizumab. This clinical trial is sponsored by the NCI. ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement. ➢ This study drug can sometimes cause autoimmune problems that can sometimes become serious or life-threatening. Getting medical treatment right away may keep these problems from becoming more serious. Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.	➢ 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. ➢ 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 _____.

PATIENTS ON STUDY ARM B (ATEZOLIZUMAB PLUS COBIMETINIB)

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 (eg, 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.

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 STUDY CHECKLIST FOR CTEP-SUPPORTED EARLY PHASE TRIALS WITH BIOMARKER ASSAYS AND BIOASSAY TEMPLATES

1. Name of marker:

CD8

2. For an integral or integrated assay, indicate the role(s) of the biomarker assay in the trial:

This is an INTEGRATED assay aimed at evaluate the effect of MEK inhibition on CD8+ T cell infiltration in patients with cholangiocarcinoma. Across many tumor types the extent of CD8+ T cell infiltration may predict clinical benefit from treatment with PD-1/PD-L1 blockade (Taube et al. 2014). Increasing CD8+ T cell infiltration is therefore one potential strategy for increasing response rates to anti-PD-1 therapies. In preclinical studies, work from the Mellman group (Ebert et al. 2016) demonstrated that MEK inhibition can reverse T cell signal-driven apoptotic ‘‘exhaustive’’ T cell death within a tumor by blocking the upregulation of certain pro-apoptotic factors resulting in the accumulation of CD8+ T cells within tumors. We postulate that MEK inhibition may represent a novel approach to re-program the tumor microenvironment in a manner that favors responsiveness to PD-L1 blockade.
In this proposal we will utilize an immunohistochemical (IHC) platform to assess CD8+ T cell infiltration in biopsy samples from patients on anti-MEK/PD-L1 combination therapy and anti-PD-L1 monotherapy. As a result of these studies, we will be able to test the following hypotheses:

- Patients with cholangiocarcinoma receiving a combination of a MEK inhibitor and a PD-L1 inhibitor will have a greater increase in CD8+ T cells in tumor than patients receiving a PD-L1 inhibitor as monotherapy.

- Greater treatment-related changes in CD8+ T cell infiltration in cholangiocarcinoma tumors will correlate with a favorable clinical response to therapy.

3. Identify the specific individual(s) and laboratory(ies) who are being considered for conducting the assay(s) for the trial.

This assay will be conducted at Johns Hopkins University. Staining for the described assay will be performed by research technicians in a Central Reference CLIA laboratory, at The Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University. Oversight of the digital analysis for this assay will be performed on the laboratory of Dr. Robert Anders. PI oversight will be performed by Dr. Mark Yarchoan and Dr. Nilo Azad.

4. Biomarker assay templates

The CD8 IHC biomarker assay template has been completed and is appended to the end of this section.

Staining for the proposed biomarker has been optimized at the Johns Hopkins Central Reference CLIA laboratory for standard clinical practice across multiple solid tumor types. In order to optimize and validate this assay, this laboratory has performed test runs of more than 50 samples in duplicate that included multiple samples tumors with high lymphocytic infiltrate (kidney cancer, melanoma, tonsil tissue), and samples from multiple tumor types with less apparent infiltrates (MSS colon cancer, pancreatic cancer). The described analyses have now been validated and successfully performed on hundreds of clinical samples at Johns Hopkins. The group at Johns Hopkins that will perform this assay has rigorously validated and previously published with this assay (Le et al. 2016, Lutz et al. 2014, N Cuka, HA Hempel, KS Sfanos, AM De Marzo 2014, Thompson et al. 2017). As with most IHC the reactions are run to saturation, thus there is little range of intensity as lymphocytes are either positive or negative. The described assay will only be performed at a single institution (Johns Hopkins University).

5. Provide data on the clinical utility of the integral/integrated assay as it will be used in the trial:

Preclinical data demonstrate the potential for synergy between MEK inhibitors and PD-1 checkpoint inhibitors. Several studies have demonstrated that MEK inhibitors upregulate HLA and downregulate certain immunosuppressive mechanisms within the tumor (Kakavand et al. 2015; Liu et al. 2015; Reddy et al. 2016). Additionally, Mellman et al. recently demonstrated that MEK inhibition may also directly potentiate T-cell based anti-tumor immunity. In an animal model, this group showed that MEK inhibition can reverse T cell signal-driven apoptotic ‘‘exhaustive’’ T cell death within a tumor by blocking the upregulation of certain pro-apoptotic factors; this results in the accumulation of CD8+ T cells within tumors. In the aggregate these data provide mechanistic rationale for combination treatment with a MEK inhibitor and an immunomodulator targeting PD-1. These data support the use of CD8+ T cell infiltration as a biomarker that may be relevant to this treatment combination.

Based on previous clinical experience, we anticipate that paired biopsy samples will be successfully obtained in at least 50% of participants. We anticipate obtaining approximately 20 subjects in each treatment arm with paired samples available for analysis, offering 80% power for detecting an increase in CD8+ density equal to 0.8s.d., using a one-sided t-test with alpha=0.05, and more than 90% power for detecting an effect size of 1.0s.d. The change in CD8 density will be captured and reported as a continuous variable, rather than a categorical variable.

As the described biomarker results are experimental in this context and are not currently applicable to the care of the patient, they will not be made available to the treating physicians or patients.

The IHC bioassay template is attached to this protocol.

APPENDIX D IMMUNE-RELATED RESPONSE CRITERIA

Introduction

Increasing clinical experience indicates that traditional response criteria (*e.g.*, Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to fully characterize activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (*i.e.*, ipilimumab) (Wolchok *et al*., 2009). (Note: The irRC only index and measurable new lesions are taken into account.)

Glossary

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

Baseline Assessment Using irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_{i} (\text{Largest diameter of lesion i}) \times (\text{Second largest diameter of lesion i})$$

Post-Baseline Assessments Using irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions (≥5 × 5 mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

Tumor burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥4 weeks from the date first documented
irPR	Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment ≥4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥25% relative to nadir confirmed by a consecutive assessment ≥4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Determination of irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

APPENDIX E PATIENT MEDICATION 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 Signature			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
_____