NCI Protocol #: 10476
Version Date: October 9, 2023

To: CTEP Protocol and Information Office

From: Nilofer Azad, M.D.

Date: October 9, 2023

Re: Amendment in response to Dr. [redacted] request for rapid amendment dated 9/29/23.

SUMMARY OF CHANGES – Protocol

I. Response to a RRA from Dr. [redacted], dated 09/29/2023:

#	Section	Comments
1.	Header, Title Page	Updated protocol version.
2.	7.1.2, 7.3	Updated instructions for managing specific AEs for Atezolizumab.
3.	10.1.1.1	Revised Atezolizumab CAEPR.

SUMMARY OF CHANGES – Consent Form:

#	Section	Comments
1.	Header	Updated protocol version.
2.	What possible risks can I expect from taking part in this study?	Added risks to Atezolizumab Rare, And Serious: • Damage to organs in the body when the body produces too many white cells • Abnormal movement of the facial muscles • Swelling of the spinal cord

NCI Protocol #: 10476

Local Protocol #: ETCTN10476

ClinicalTrials.gov Identifier: NCT04941287

TITLE: A Randomized Phase 2 Study of Combination Atezolizumab and CDX-1127 (Varlilumab) With or Without Addition of Cobimetinib in Previously Treated Unresectable Biliary Tract Cancers

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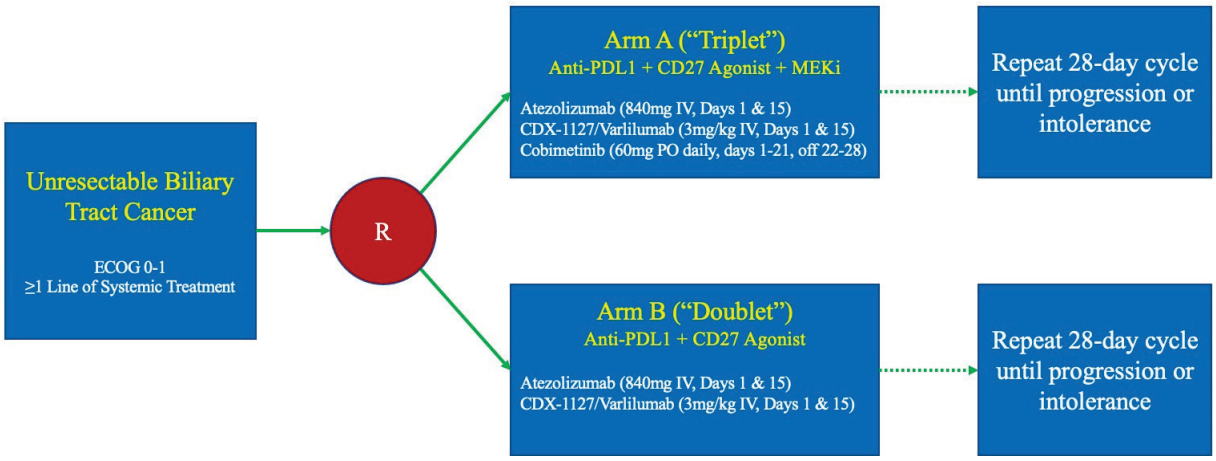
NCI-Supplied Agents: CDX-1127 (varlilumab) (NSC 778372), Atezolizumab (NSC 783608), and Cobimetinib (NSC 781257)

[redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:	Original / February 23, 2021 Revision 1 / April 23, 2021 Revision 2 / May 24, 2021 Revision 3a / July 6, 2021 Revision 3b / August 4, 2021 Amendment 1 / October 30, 2021 Amendment 2/ December 8, 2021 Amendment 3/ January 28, 2022 Amendment 4 / April 26, 2022 Amendment 5 / July 18, 2022 Amendment 6 / November 1, 2022 Amendment 7 / October 9, 2023

SCHEMA



Stratification Factor:

Site of Disease (Gallbladder cancer (GBC) vs. Intrahepatic cancer (IHC) vs. Extrahepatic cholangiocarcinoma (EHC))

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the response rate (ORR) of patients with unresectable, pre-treated biliary cancers treated with the combination of atezolizumab and CDX-1127 (varlilumab) with or without cobimetinib.

1.1.2 To assess the progression free survival (PFS) of patients with unresectable, pre-treated biliary cancers treated with the combination of atezolizumab and CDX-1127 (varlilumab) with or without cobimetinib

1.2 Secondary Objectives

1.2.1 To assess the safety and tolerability of combination of atezolizumab and CDX-1127 (varlilumab) with or without cobimetinib in patients with unresectable, pre-treated biliary cancers.

1.2.2 To assess overall survival (OS) of patients with unresectable, pre-treated biliary cancers treated with the combination of atezolizumab and CDX-1127 (varlilumab) with or without cobimetinib.

1.2.3 To determine the effect of combination atezolizumab and CDX-1127 (varlilumab) +/- cobimetinib on T cell subpopulations systemically and intratumorally.

2. BACKGROUND

2.1 Study Disease(s)

Biliary Tract Cancer (BTC) refers to a group of heterogenous malignancies arising from biliary epithelial cells along different sites of the biliary tree that include intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC). Overall survival for this disease, even when including resectable patients, is poor with less than 5% of patients living beyond 5 years (Shaib and El Serag, 2004). Unresectable CCA patients treated with standard frontline therapy, gemcitabine plus cisplatin, have a median overall survival (OS) of less than one year (Valle *et al.*, 2010). The benefit of cytotoxic chemotherapy in the second line setting is small, underscoring the need for additional treatment options for these patients (Lamarca *et al.*, 2014; Rogers *et al.*, 2014; Lamarca *et al.*, 2019). Inhibition of programmed cell death protein 1 (PD-1) or its ligand (PD-LD1) has shown limited clinical activity in BTC as monotherapy, with response rates of approximately 5-11% in the largest reported prospective clinical trials (Ueno *et al.*, 2019; Ioka *et al.*, 2019; Ueno *et al.*, 2018; Kim *et al.*, 2020). The development of novel therapeutic combinations that can extend the clinical benefit of ICIs to immunologically resistant tumors such as BTC remains a significant challenge.

2.2 CTEP IND Agents

2.2.1 **Atezolizumab**

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells (Investigator's Brochure, 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 Mechanism of Action

PD-L1 expression is prevalent in many human tumors (*e.g.*, lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (Thompson *et al.*, 2006; Hamanashi *et al.*, 2007; Okazaki and Honjo 2007;

Hino *et al.*, 2010). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1), and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer (Blank *et al.*, 2005; Keir *et al.*, 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen, 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

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

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

2.2.1.2 Summary of Nonclinical Experience

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

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

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

2.2.1.3 Summary of Clinical Experience

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

2.2.1.3.1 Clinical PK and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab shows linear PK at doses ≥1 mg/kg (Investigator's Brochure, 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 10.1.1.1.

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 (GDC-0973, XL518) is a low-molecular weight, orally available, potent non-ATP-competitive inhibitor of MEK1 and MEK2 (Choo *et al.* 2012). Selectivity of cobimetinib has been demonstrated in biochemical, cell-based, and in vivo assays (Hatzivassiliou *et al.* 2013; Hoeflich *et al.* 2012; Wong *et al.* 2012; Musib *et al.* 2013). As rationale for its development, the inhibition of MEK has been shown to be a promising strategy to control the growth of tumors dependent on aberrant signaling in the Ras/RAF pathway (Hoeflich *et al.* 2012).

2.2.2.1 Summary of Nonclinical Experience

Nonclinical data show that cobimetinib is a potent and highly selective inhibitor of MEK1/2, resulting in inhibition of cellular phosphorylation of ERK1/2 and anti-proliferative activity in a variety of human tumor cell lines and tumor xenograft models. Cobimetinib accumulates in tumor xenografts and remains at high concentrations in the tumor after

plasma concentrations have declined. The inhibition of ERK1 phosphorylation by cobimetinib correlates more closely with concentrations of cobimetinib in tumor tissues than in plasma; in general, there is a good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models. The findings of in vitro and in vivo nonclinical safety pharmacology studies indicated that there was a low potential for cardiovascular (CVS), neurobehavioral, or respiratory function in patients (Investigator's Brochure, 2019).

Nonclinical and in vitro metabolic profiling studies suggest that cobimetinib is a substrate for CYP3A4 and UGT2B7-mediated metabolism in human liver microsomes and recombinant enzymes; cobimetinib is an inhibitor of isozymes CYP2D6 and CYP3A4 in vitro. Cobimetinib is approximately 95% bound to human plasma proteins. The pharmacokinetics of cobimetinib has been characterized in multiple species including mice, rats, dogs, and monkeys (Investigator's Brochure, 2019).

The nonclinical toxicity of cobimetinib was characterized in single-dose and repeat-dose studies in rats and dogs, repeat-dose toxicity study in juvenile rats, reproductive and developmental studies in rats, genotoxicity studies including in vitro bacterial and mammalian genotoxicity bioassays and in vivo micronucleus assay in rats, and in vitro (3T3 mouse fibroblasts) and in vivo (pigmented rats) phototoxicity studies. The nonclinical safety assessment for cobimetinib identified degenerative effects in multiple tissues that are clinically manageable and the potential for reproductive toxicity at therapeutically relevant exposures. It was not phototoxic or genotoxic in vitro or in vivo. When considered together with the clinical safety database and the intended treatment population, the results of the nonclinical toxicity program provide a safety profile that supports the use of cobimetinib in the treatment of cancers.

2.2.2.2 Summary of Clinical Experience

The following are key clinical trials in the cobimetinib clinical development program for melanoma.

2.2.2.2.1 Cobimetinib Monotherapy

Study MEK4592g was a multicenter, Phase 1, single-agent dose escalation study. The primary objectives of this study were to evaluate the safety, tolerability, and maximum tolerated dose (MTD) of cobimetinib administered orally as repeated doses in patients with solid tumors.

In Stage I, 36 patients with advanced solid malignancies were enrolled in successive cohorts and received cobimetinib on a 21-day on, 7-day off (21/7) dosing schedule at the following dose levels: 0.05 mg/kg, 0.10 mg/kg, and 0.20 mg/kg in liquid dosage formulation and 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg in capsule formulation (Cohorts 1-8, respectively). The MTD is 60 mg on a 21/7 dosing schedule.

In Stage IA, 20 patients were treated with cobimetinib on a 14-day on, 14-day off (14/14) dosing schedule in successive cohorts at the following dose levels: 60 mg, 80 mg, 100 mg, and 125 mg in capsule formulation (Cohorts 1A-4A, respectively). The MTD is 100 mg on a 14/14 dosing schedule.

Stages II and IIA are expansion stages that further evaluate the safety, potential efficacy, and pharmacodynamic effects of cobimetinib at the MTDs determined in Stage I and Stage IA in patients with Ras- or RAF-mutant tumors. In Stage II, 20 patients were enrolled and received 60 mg cobimetinib on a 21/7 dosing schedule. In Stage IIA, 21 patients were enrolled and received 100 mg cobimetinib on a 14/14 dosing schedule. In Stage II, the dedicated DDI study, 20 patients with solid tumors received 60 mg daily (QD) 21/17.

2.2.2.2.2 Combination of Cobimetinib with Vemurafenib in Melanoma

The objective of the clinical investigation of the combination of vemurafenib with GDC-0973 (MEK inhibitor) is to simultaneously inhibit both oncogenic BRAF kinase (vemurafenib) and MEK (GDC-0973) in patients with previously untreated, BRAFV600E mutation-positive, locally advanced and unresectable or metastatic melanoma, OR those previously treated with vemurafenib in Phase 1 (PLX06-02, clinical pharmacology), Phase 2, and Phase 3 clinical trials, with evidence of mixed progression.

Phase 1b Open-Label Cobimetinib and Vemurafenib Study (NO25395; BRIM-7)
Study NO25395 (BRIM-7) was a Phase 1b study designed to assess the safety, tolerability, and pharmacokinetics of combined MEK inhibition with cobimetinib and BRAF inhibition with vemurafenib. This multicenter study had two stages: a dose-escalation stage and a cohort-expansion stage.

All patients in the dose-escalation stage received vemurafenib (720 mg or 960 mg) twice daily (BID) in combination with cobimetinib (60 mg, 80 mg, or 100 mg) administered daily according to one of the following 28-day schedules:
- 14 consecutive days of study drug followed by a 14-day drug holiday (14/14)
- 21 consecutive days of study drug followed by a 7-day drug holiday (21/7)
- Continuous daily dose (28/0)

Cohorts 1A and 1B were expansion cohorts because both cohorts were declared safe and tolerable after dose escalation; furthermore, they delivered the single-agent maximum tolerated dose and schedule of cobimetinib and, in the case of Cohort 1B, the approved dose and schedule of vemurafenib (Ribas *et al*. 2014a; Ribas *et al*. 2014b; Pavlick *et al*. 2015).

Randomized Phase 3 Study of Vemurafenib and Cobimetinib (GO28141; CoBRIM)
This randomized, open-label, multicenter, Phase 3 study assessed previously untreated patients with metastatic melanoma confirmed by histopathology (unresectable stage IIIC or stage IV) and with a BRAFV600 mutation by the Cobas® 4800 $BRAF^{V600}$ Mutation Test (Larkin *et al*. 2014). In this study, 495 patients were randomly assigned to receive vemurafenib (960 mg BID orally [PO]) and cobimetinib (60 mg QD PO) for the first 21 days of each 28-day cycle (combination group) or vemurafenib and placebo (control group). The primary endpoint was investigator-assessed PFS according to RECIST version 1.1. The secondary endpoints included overall survival (OS), rate of confirmed objective response, DOR, IRC-assessed PFS, and safety. The final analysis was planned to occur after 206 events, which was reached in May 2014. The initial results were reported based on data analyses from July 2014 after the pre-specified number of progression events was reached in May 2014 (Larkin *et al*. 2014). Updated results were

presented at American Society of Clinical Oncology (ASCO) 2015 (Larkin *et al*. 2015) based on a data cutoff date of January 16, 2015.

Vemurafenib plus cobimetinib was significantly superior to vemurafenib alone: median PFS was 12.3 months in the combination group and 7.2 months in the vemurafenib group (HR=0.58; 95% CI: 0.46, 0.72). The PFS benefit was observed across key subgroups including LDH levels and BRAF mutation type. ORR was 69.9% (95% CI: 63.5%, 75.3%) with 15.8% CRs in the combination arm and 50% (95% CI: 43.6%, 56.4%) with 10.5% CRs in the single-agent arm (Larkin *et al*. 2015). After 255 patient deaths, the median OS was 22.3 months (95% CI: 20.3-not estimable) for the combination group and 17.4 months (95% CI: 15.0-19.8) for the monotherapy group, with a hazard ratio (HR) of 0.70 (95% CI: 0.55-0.90; *P*=0.005) (Ascierto *et al*. 2016).

2.2.2.2.3 Clinical Safety Summary

Cobimetinib Monotherapy

As of the data cutoff date of June 11, 2013, 115 patients were treated across all study stages in Study MEK4592g (single agent cobimetinib), including 74 patients treated with cobimetinib 60 mg 21/7.

All patients in Study MEK4592g experienced an adverse event (AE). The most frequent AEs were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea, 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.

Amongst the patients who received cobimetinib 60 mg 21/7, the most frequent treatment emergent AEs in the cobimetinib 60 mg QD 21/7 group were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea, edema peripheral (31.1% each), and vomiting (28.9%).

Amongst all cobimetinib-treated patients, 5 patients (4.3%) experienced a Grade 4 AE, and 53 patients (46.1%) experienced a Grade 3 AE. The most frequent Grade 3 and Grade 4 AEs were hyponatremia (9.6%), fatigue (8.7%), anemia (7.8%), diarrhea, and hypokalemia (6.1% each). Grade 5 AEs, which in Study MEK4592g included disease progression reported as an AE, are discussed separately below.

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

As of the clinical-data cutoff date (20 September 2013), a total of 29 patients (25.2%) had died, including 11 patients in the cobimetinib 60 mg QD 21/7 group. A total of 14 deaths were

reported for patients treated in Stage I of the study. With the exception of 1 patient who died of cardiopulmonary arrest secondary to progressive disease (PD), all Stage I deaths occurred because of PD and no death was considered by the investigator to be related to the study drug.

During Stages IA, II, and IIA of the study, 12 deaths were reported, all of which occurred ≤30 days after the last dose of study drug. Of these, 2 deaths were considered by the investigator to be possibly related to study drug. In both cases, the investigator considered the metastatic cancer to be a contributing etiologic factor to the patient's death.

Three deaths were reported in Stage III of this study. None was assessed by the investigator as treatment related. Other contributing etiologic factors to the deaths included the patients' underlying diseases and malignant tumor progression

Adverse events of special interest for cobimetinib monotherapy (without vemurafenib) include the following. Details of these events are described in the section for the combination of vemurafenib and cobimetinib. A comprehensive list of AEs related to cobimetinib is included in CAEPR.

Adverse Events of Interest:
Hemorrhage: Hemorrhage, including major hemorrhages defined (symptomatic bleeding in a critical area or organ), can occur with cobimetinib. Events observed included cerebral hemorrhage, GI hemorrhage, reproductive tract hemorrhage, and hematuria.

In randomized phase 3 trial of cobimetinib + vemurafenib *vs.* vemurafenib-placebo, hemorrhagic events were 13.0% with cobimetinib + vemurafenib *vs.* 7.3% with vemurafenib. Grade 3 to 4 hemorrhage occurred in 1.2% *vs.* 0.8% of patients. Increased hemorrhage was seen in several sites: cerebral hemorrhage (0.8% *vs.* 0), gastrointestinal tract hemorrhage (3.6% *vs.* 1.2%), reproductive system hemorrhage (2.0% *vs.* 0.4%), and hematuria (2.4% *vs.* 0.8%).

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

Cardiomyopathy: Cardiomyopathy, defined as symptomatic and asymptomatic decline in left ventricular ejection fraction (LVEF), can occur with cobimetinib. The safety of cobimetinib has not been established in patients with a baseline LVEF that is either below institutional lower limit of normal (LLN) or below 50%. In randomized phase 3 trial of cobimetinib + vemurafenib *vs.* vemurafenib + placebo, patients were assessed for LVEF by echocardiograms or multiple-gated acquisition (MUGA) at baseline, Week 5, Week 17, Week 29, Week 43, and then every 4 to 6 months thereafter while receiving treatment.

Grade 2 or 3 decrease in LVEF occurred in 26% *vs.* 19% of patients receiving the combination *vs.* vemurafenib. The median time to first onset of LVEF decrease was 4 months (range: 23 days to 13 months). Two patients on the combination arm (0.8%) were symptomatic

Of the patients with decreased LVEF, 22% had dose interruption and/or reduction and 14%

required permanent discontinuation. Decreased LVEF resolved to above the LLN or within 10% of baseline in 62% of patients receiving cobimetinib with a median time to resolution of 3 months (range: 4 days to 12 months).

Serous Retinopathy and Retinal Vein Occlusion: Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK inhibitors, including cobimetinib. In the randomized phase 3 trial of cobimetinib-vemurafenib *vs.* vemurafenib-placebo, ophthalmologic examinations including retinal evaluation were performed pretreatment and at regular intervals during treatment.

Symptomatic and asymptomatic serous retinopathy was identified in 26% of patients receiving cobimetinib and vemurafenib. The majority of these events were reported as chorioretinopathy (13%) or retinal detachment (12%). The time to first onset of serous retinopathy events ranged between 2 days to 9 months. The reported duration of serous retinopathy ranged from 1 day to 15 months. One patient in each arm developed retinal vein occlusion. Perform an ophthalmological evaluation at regular intervals and any time a patient reports new or worsening visual disturbances.

CPK elevation and rhabdomyolysis: Elevations in creatine phosphokinase (CPK) have been observed in patients treated with cobimetinib monotherapy. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. In Study GO28141 (cobimetinib-vemurafenib *vs.* vemurafenib), elevated CPK was more frequent in the combination arm, (32.4% *vs.* 8.1% all grades, 11.3% *vs.* 0 > G3). CPK increase of more than 10 times the baseline value with a concurrent increase in serum creatinine >1.5 times of baseline occurred in 3.6% of patients receiving combination and in 0.4% of patients receiving vemurafenib. The median time to first occurrence of Grade 3 or 4 CPK elevations was 16 days (range: 12 days to 11 months); the median time to complete resolution was 15 days (range: 9 days to 11 months).

One event of rhabdomyolysis was reported in the Phase 3 study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience.

Rash and Skin reactions: Severe rash and other skin reactions can occur with cobimetinib. In the Phase 3 study GO28141 (phase 3 cobimetinib-vemurafenib *vs.* vemurafenib), combined rash events of all types and grades were more frequent (71.7% *vs.* 66.7%), although Grade ≥3 events (approximately 16%) and types of rash were similar between arms. Grade 4 rash in 1.6% *vs.* 0.8%. Specific events included rash (39% all grades, 5.9% Grade ≥3, 1.6% SAE) and rash maculo-papular (14.6% all grades, 6.3% Grade ≥3, 1.2% SAE).

The median time to onset of Grade 3 or 4 rash events was 11 days (range: 3 days to 2.8 months). Among patients with Grade 3 or 4 rash events, 95% experienced complete resolution with the median time to resolution of 21 days (range 4 days to 17 months). Generally, Grade ≥3 rash events were effectively managed with dose modification guidelines. Approximately 90% of Grade ≥3 rash events resolved in both arms.

Hepatotoxicity: Hepatotoxicity can occur with cobimetinib.
In the Phase 3 study GO28141 (cobimetinib-vemurafenib *vs.* vemurafenib), Grade 3 or 4 liver laboratory (LFT) abnormalities in the cobimetinib-vemurafenib arm compared to vemurafenib were 20.5% *vs.* 15.1%, including 11% *vs.* 5% for alanine aminotransferase, 8% *vs.* 2.1% for aspartate aminotransferase, 1.6% *vs.* 1.2% for total bilirubin, and 7% *vs.* 3.3% for alkaline phosphatase. In one (0.4%) *vs.* no patient receiving combination *vs.* vemurafenib alone, there was concurrent elevation in ALT >3 times the upper limit of normal (ULN) and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >2 X ULN occurred.

In the Phase 3 study GO28141, in cobimetinib + vemurafenib or vemurafenib arm, the majority of Grade ≥3 liver laboratory test abnormalities resolved.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal reproduction studies, cobimetinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during the period of organogenesis was teratogenic and embryotoxic at doses resulting in exposures [area under the curves (AUCs)] that were 0.9 to 1.4-times those observed in humans at the recommended human dose of 60 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with cobimetinib, and for 3 months following the final dose of cobimetinib.

2.2.2.2.4 Clinical Pharmacokinetics of Cobimetinib

Cobimetinib pharmacokinetics has been characterized in cancer patients following oral administration after single and multiple dosing in the Phase 1a dose-escalation study (MEK4592g). Cobimetinib showed high variability in pharmacokinetic parameters.
The pharmacokinetics of cobimetinib was studied in healthy subjects and cancer patients. Cobimetinib exhibits linear pharmacokinetics in the dose range of 3.5 to 100 mg (i.e., 0.06 to 1.7 times the recommended dosage). Following oral administration of COTELLIC 60 mg once daily, steady-state was reached by 9 days with a mean accumulation ratio of 2.4-fold (44% CV).

Absorption: Following oral dosing of 60 mg once daily in cancer patients, the median time to achieve peak plasma levels (T_{max}) was 2.4 (range:1–24) hours, geometric mean steady-state $AUC_{0\text{-}24h}$ was 4340 ng·h/mL (61% CV) and the maximum plasma concentration (C_{max}) was 273 ng/mL (60% CV). The absolute bioavailability of COTELLIC was 46% (90% CI: 40%, 53%) in healthy subjects. A high-fat meal (comprised of approximately 150 calories from protein, 250 calories from carbohydrate, and 500–600 calories from fat) had no effect on cobimetinib AUC and C_{max} after a single 20 mg COTELLIC was administered to healthy subjects.

Distribution: Cobimetinib is 95% bound to human plasma proteins in vitro, independent of drug concentration. No preferential binding to human red blood cells was observed (blood to plasma ratio of 0.93). The estimated apparent volume of distribution was 806 L in cancer patients based on a population PK analysis.

Elimination: Following oral administration of COTELLIC 60 mg once daily in cancer patients, the mean elimination half-life ($t_{1/2}$) was 44 (range: 23–70) hours and the mean apparent clearance

(CL/F) was 13.8 L/h (61% CV).

Metabolism: CYP3A oxidation and UGT2B7 glucuronidation were the major pathways of cobimetinib metabolism in vitro. Following oral administration of a single 20 mg radiolabeled cobimetinib dose, no oxidative metabolites >10% of total circulating radioactivity were observed.

Excretion: Following oral administration of a single 20 mg radiolabeled cobimetinib dose, 76% of the dose was recovered in the feces (with 6.6% as unchanged drug) and 17.8% of the dose was recovered in the urine (with 1.6% as unchanged drug).

2.2.2.2.5 Cobimetinib Drug Interactions

In vitro studies showed that **cobimetinib is a time-dependent inhibitor of CYP3A and a competitive inhibitor of CYP2D6**. In vitro studies also show that **cobimetinib is a substrate of CYP3A and UGT2B7**.

Effect of Strong or Moderate CYP3A Inhibitors on Cobimetinib
Coadministration of cobimetinib with itraconazole (a strong CYP3A4 inhibitor) increased cobimetinib systemic exposure by 6.7-fold. 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 for patients who are taking cobimetinib 60 mg, reduce cobimetinib dose to 20 mg. After discontinuation of a moderate CYP3A inhibitor, resume cobimetinib at the previous dose.

Use an alternative to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of cobimetinib (40 or 20 mg daily)

Effect of Strong or Moderate CYP3A Inducers on Cobimetinib: 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

Effect of Cobimetinib on CYP Substrates: Coadministration of cobimetinib 60 mg once daily for 15 days with a single 30 mg dose of dextromethorphan (sensitive CYP2D6 substrate) or a single 2 mg dose of midazolam (sensitive CYP3A substrate) to 20 patients with solid tumors did not change dextromethorphan or midazolam systemic exposure. In vitro data indicated that cobimetinib may inhibit CYP3A and CYP2D6. Cobimetinib at clinically relevant concentrations is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9 and 2C19 or inducer of CYP1A2, 2B6 and 3A4.

Effect of Transporters on Cobimetinib: 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.

Effect of Cobimetinib on Transporters: In vitro data suggest that cobimetinib at clinically relevant concentrations does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or OCT2.

Effect of Gastric Acid Reducing Drugs on Cobimetinib: 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.

2.2.3 CDX-1127 (varlilumab)

CDX-1127 (varlilumab) is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds human CD27 (Investigator's Brochure, 2020). The costimulatory molecule CD27 is a member of the tumor necrosis factor (TNF) receptor superfamily and is constitutively expressed on the majority of mature T cells, memory B cells, and a portion of natural killer (NK) cells. The interaction of CD27 with its ligand CD70 plays key roles in the following processes:

- Costimulation through CD27 on T cells promotes activation, proliferation, survival, and maturation of effector capacity and memory
- Costimulation through CD27 on human B cells has also been implicated to promote proliferation, the production of immunoglobulin, and generation of plasma cells
- Costimulation through CD27 on NK cells induces cytolytic activity

The importance of this pathway is highlighted by rare individuals that are characterized with CD27 deficiency that arise due to genetic alterations and are associated with uncontrolled Epstein Barr virus infections and other disorders (Alkhairy, *et al.* 2015, van Montfrans, *et al.* 2012).

[redacted]

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[redacted]

2.3 Rationale

2.3.1 Atezolizumab (anti-PDL1) plus Cobimetinib (MEK inhibitor) in BTC (NCI10139)

MEK inhibitors have shown immunomodulatory effects and substantial efficacy when combined with PD-(L)1 inhibitors in multiple preclinical models (Peng *et al.*, 2020; Dushyanthen *et al.*, 2020; Ebert *et al.*, 2016). Targeting of the MAPK pathway through MEKi is hypothesized to modulate the tumor immune microenvironment (TME) through effects on both tumor cells and direct effects on immune cells, resulting in enhanced major histocompatibility complex class I (MHC-1) expression and CD8+ T cell infiltration (Dushyanthen *et al.*, 2020; Hellmann *et al.*, 2019; Liu *et al.*, 2015; Brea *et al.*, 2016; Caunt *et al.*, 2015; Mimura *et al.*, 2013; Angell *et al.*, 2014). The combination of a MEK inhibitor (cobimetinib) plus a PD-L1 inhibitor (atezolizumab) failed to show compelling immune activity in a large phase 3 clinical study in colon cancer (Bendell *et al.*, 2018), however a therapeutic signal was demonstrated in our CTEP-sponsored trial of this strategy trial in BTC patients, the largest randomized immunotherapy trial to date in BTC [20]. Presented as a plenary at AACR 2020, our group reported the results of the ETCTN randomized phase 2 trial of atezolizumab as monotherapy or in combination with the MEK inhibitor cobimetinib in heavily pretreated advanced BTC patients (N=77) (Yarchoan, *et al.*, 2020a). The trial met its primary endpoint, with a median PFS of 3.65 months in the atezolizumab plus cobimetinib combination arm, versus 1.87 months in the atezolizumab monotherapy arm (p=0.027). However, only one patient in each had a RECIST criteria partial response, suggesting that optimization of the strategy of immunomodulation through MEK inhibition is still needed. Importantly, the combination was tolerable without significant differences in discontinuation compared to the single agent arm due to adverse events. Correlative studies utilizing a limited number of paired tumor biopsies demonstrated that treatment with cobimetinib resulted in an increase in CD8+ T cell to FoxP3+ regulatory T cell

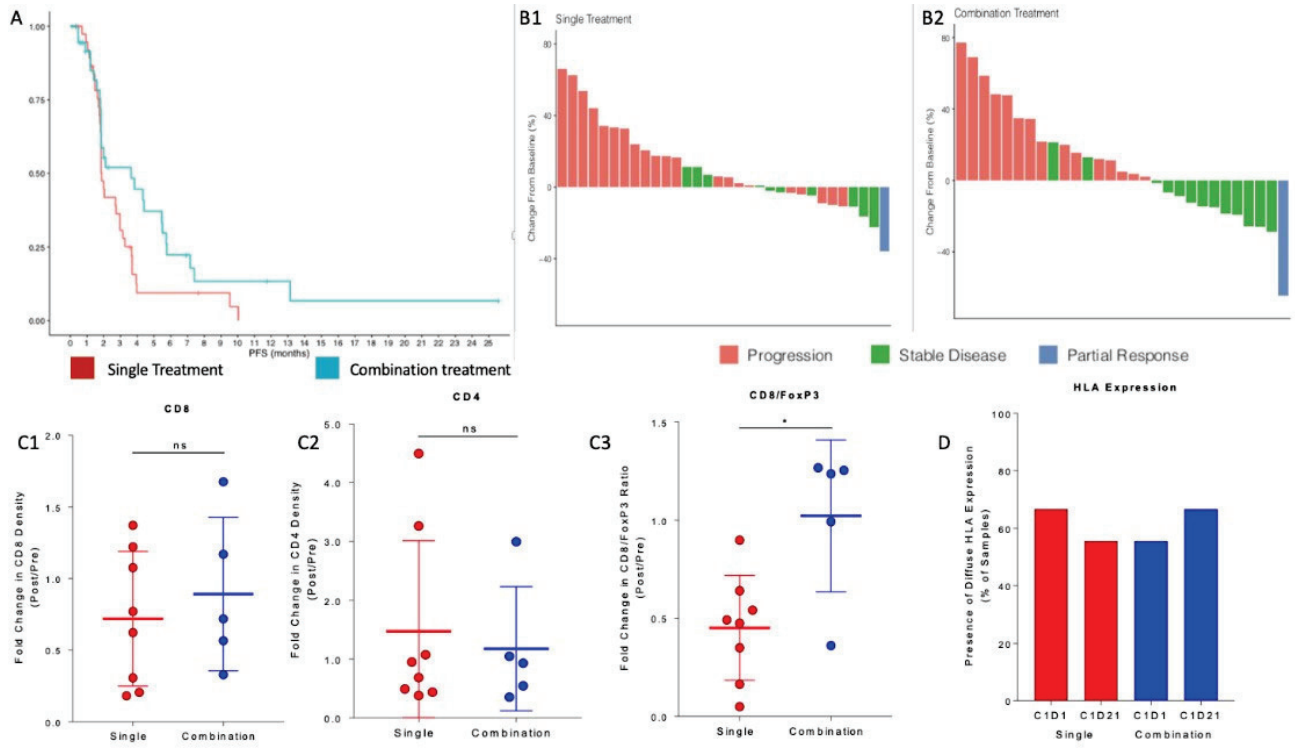


Figure 1: Clinical and immunologic response in BTC patients treated with atezolizumab (Atezo) with or without cobimetinib (Cobi). PFS Kaplan Meier curve of Atezo + Cobi compared to Atezo alone showing a significant prolongation in PFS (p=0.027); B) Waterfall plot of tumor response of respective trial arms Atezo alone [B1] and Atezo + Cobi [B2]; C) Fold changes in TIL composition of CD8+ [C1], CD4+ [C2], CD8+:FOXP3 ratio [C3]; D) HLA expression of sample at days 1 & 21 of first cycle Atezo + Cobi vs. Atezo alone (Yarchoan, *et al.*, 2020b).

ratio, supporting the hypothesis that MEK inhibition can prime a cancer to become a checkpoint sensitive tumor (see Figure 1) (Yarchoan, *et al.*, 2020b).

2.3.2 MEKi plus anti-PDL1

Although our randomized study of cobimetinib plus atezolizumab demonstrated that the combination therapy is tolerable and can prolong PFS in BTC, additional therapies in combination may be necessary to induce more compelling response rates in patients. Unpublished ongoing work from our group and other groups have further interrogated the mechanisms of immunomodulation with MEK inhibitors, using both commercially available genetic tools and small molecular MEK inhibitors in tumor models. Using a MEK1 knock-out RAS-driven tumor model (CT26 MEK1 KO), we find that MEK1 inhibition reprograms the tumor immune microenvironment, enhancing JAK/STAT1 signaling and antigen presentation in tumor cells, enhanced CD8+ T cell activation and IFNγ and granzyme B expression, and markedly prolonging survival in immune competent mice (Figure 2).

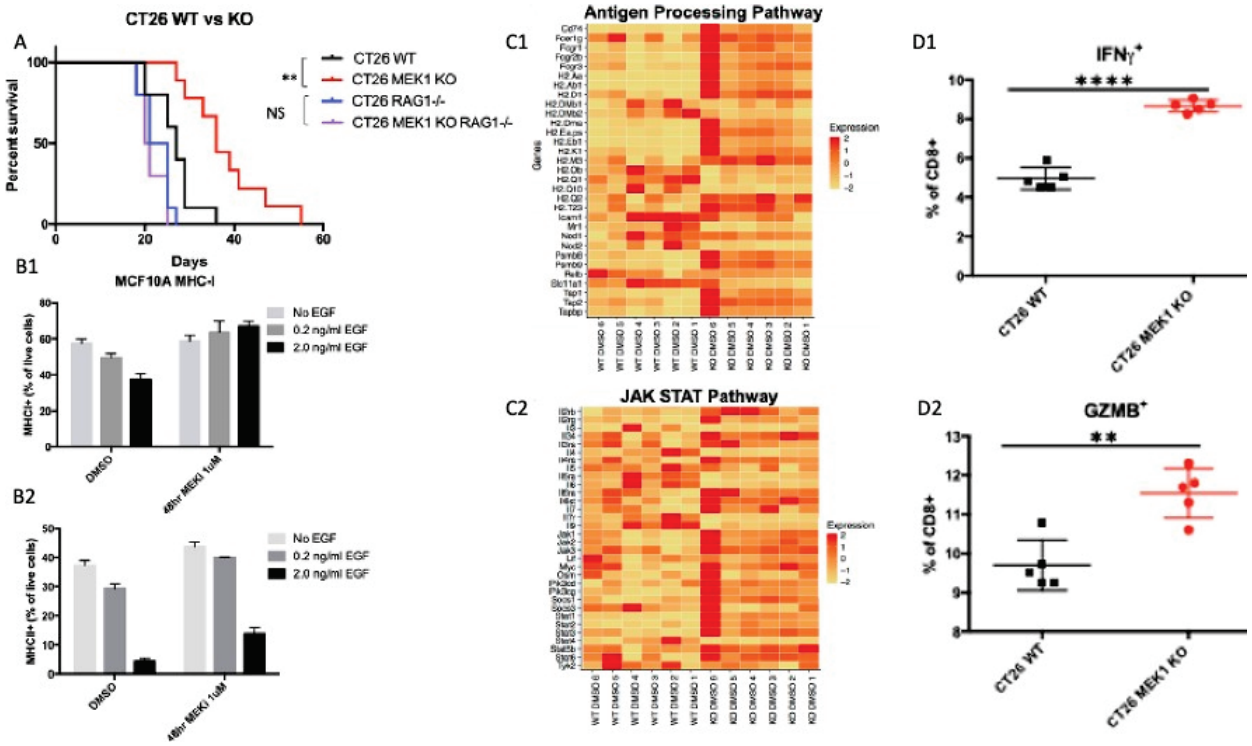


Figure 2: Genetic knockout of MEK1 in tumor cells augments immune responses in mice bearing RAS-driving malignancy. A) CT26 MEK1 KO impairs tumor growth in vivo in an immune-competent mouse, but has no effect on tumor growth in an immune-compromised RAG-KO mouse; B) Activation of the MAPK pathway through EGF leads to downregulation of MHCI [B1] and MHCII [B2], but cobimetinib reversed this by increasing MHC I/II presentation thus supporting MAPK signaling negatively regulating MHCI and MHCII; C) MEK1 KO tumors (CT26 background) upregulated antigen processing [C1] and the JAK STAT pathway [C2] D) MEK1 KO tumors (CT26 background) had increased numbers effector T cell infiltration and markers of effector proliferation, and function (Dennison & Yarchoan, Unpublished)

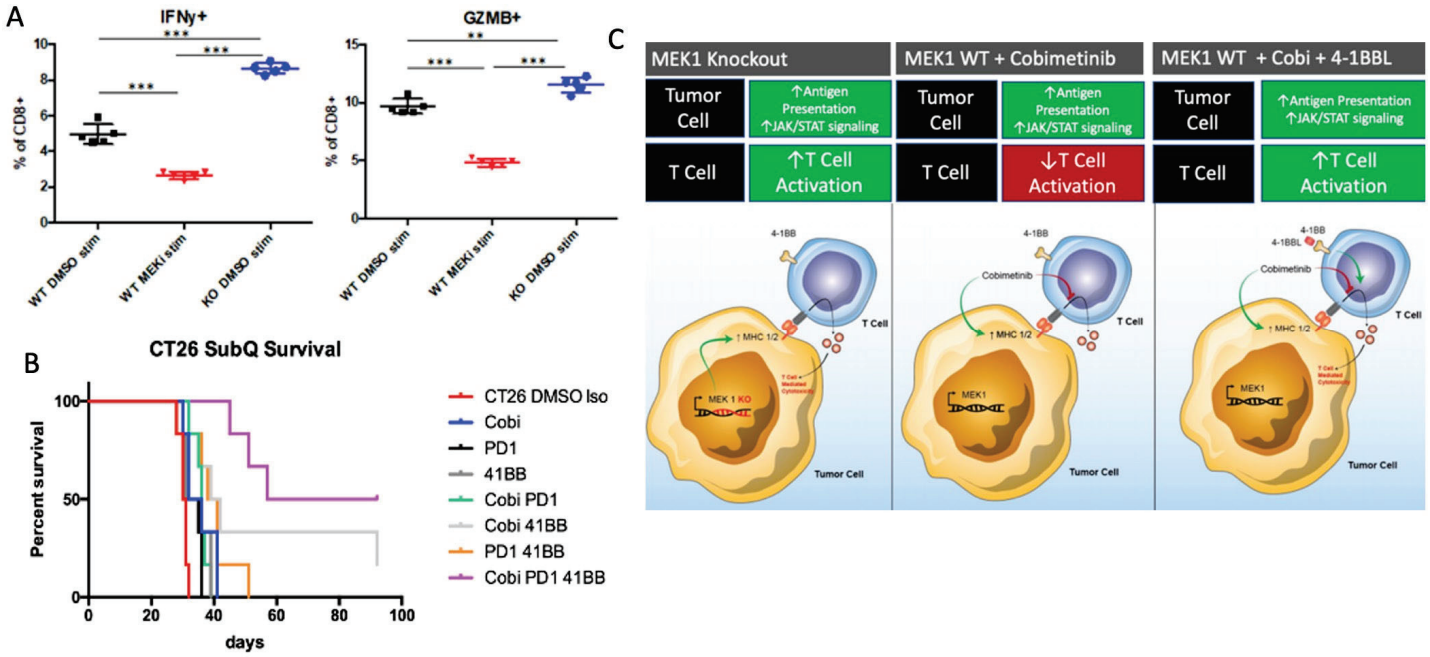


Figure 3: Impaired T cell response after MEKi treatment can be rescued by addition of 4-1BBL. A) Percentage of CD8+ cells expression INFy+ and GZMB+ in WT, WT + MEKi, MEK1 KO B) Combination MEKi+Anti-PD1+ 41BBL improves survival. C) Pictorial summary of exploratory findings (Dennison & Yarchoan, Unpublished)

While MEK1 inhibition in tumor cells has uniformly positive anti-tumor immune effects in our model, the effects of systemic MEK inhibition (thereby inhibiting MEK on both tumor cells and lymphocytes) is complex. MEK is downstream of TCR signaling, and systemic MEK inhibitors may impair T cell priming and activation (Figure 3). This data may provide a potential mechanism for why dual blockade of MEK and PD-L1 has failed to induce compelling response rates in human clinical trials, and suggests the possibility that the activity of MEKi plus PD-L1 may be improved with the addition of a co-stimulatory agent that can function independently of the MAPK pathway. Our findings are consistent with the results of other groups, which consistently show that while pharmacologic MEKi relieves TME immunosuppression and facilitates accumulation of antigen-specific CD8+ TILs, it *simultaneously* impairs T cell priming, and effector proliferation/function systemically (Ebert *et al.*, 2016; Vella *et al.*, 2014). Several reports have shown that agonist therapy (OX-40, 41BBL, etc.,) restores T cell function and increases antitumor immunity mediated by MEK inhibitors with PD-L1 blockade.(Dushyanthen *et al.*, 2017; Baumann *et al.*, 2020; Allegrezza *et al.*, 2016). Consistent with this hypothesis, the addition of a costimulatory agonist, 41BB (anti-CD137), significantly prolonged survival in our preclinical model as compared all other treatment doublets/monotherapies in the CT26 tumor model. MEKi may also protect T cells against activation induced cell death, which has hampered the development of multiple agonist antibodies, further supporting the rationale for combining MEK with a stimulatory agent.

2.3.3 CD27 Agonism

Relative to the robust translational and clinical experience with ICIs, immune agonists that activate costimulatory receptors on T cells have proven to be challenging to develop despite great promise. Part of this is due to the challenges in inducing immune stimulation safely as seen with cases of cytokine release syndrome documented with CD28 agonism, and dose-limiting immunotoxicities with OX-40 and 41BBL therapies (Suntharalingam *et al.*, 2006; Yonezawa *et al.*, 2015; Vonderheide and Glennie, 2013; Ramakrishna *et al.*, 2015). Another target for immune agonists is CD27, a member of the tumor necrosis factor receptor superfamily and a costimulatory molecule on T cells (Ansell *et al.*, 2020). With engagement of its ligand CD70, CD27 promotes T-cell activation, proliferation, survival, and maturation of effector capacity as well as T-cell memory, B-cell proliferation, B-cell memory, and induces of the cytolytic activity of natural killer (NK) cells (Burris *et al.*, 2017). Notably, CD27's costimulatory effects on T cell activation/proliferation and augmentation of immune response remains cannot occur without concomitant TCR signaling. The first-in-class anti-CD27 agonist mAb, CDX-1127 (varlilumab) (CellDex), has not only demonstrated T cell activation and anti-tumor activity in preclinical models, but has shown to be safe and well-tolerated in early clinical trials of patients with advanced solid and hematologic malignancies (Ramakrishna *et al.*, 2015; Ansell *et al.*, 2020; Burris *et al.*, 2017). Pre-clinical models demonstrate that agonist antibodies targeting CD27 act synergistically with anti–PD-1/L1 to increase CD8+ T-cell proliferation, effector function, and tumor clearance through distinct but complementary gene expression mechanisms (Buchan *et al.*, 2018). Clinical trials with these therapy combinations have proven safe and well-tolerated (Ansell *et al.*, 2020; Burris *et al.*, 2017; Shapira-Frommer *et al.*, 2020). Correlative analyses of these clinical trials have showed that CDX-1127 (varlilumab) treatment activates memory CD4+ and CD8+ T cells, with a bias toward CD8+ T lymphocyte proliferation while also decreasing circulating Tregs (Ramakrishna *et al.*, 2015).

2.3.4 Rationale for MEK inhibition, PD-L1 inhibition, and CD27 agonism in BTC

Immune checkpoint inhibitors have demonstrated limited activity in BTC as monotherapy, and while the combination of MEKi plus PD-L1 improved PFS in our prior randomized phase 2 study, response rates remain low. Our unpublished preclinical work indicates that immune agonists that activate costimulatory receptors on T cells can rescue T cell activation in the setting of MEKi plus PD-L1i, resulting in improved survival. Although 41BB was used to show proof of principle in our experiments because the wide availability of murine 41BB agonists, the clinical development of 41BB agonists has been hampered by off-target toxicity. CD27 is a more compelling agonist because of the established safety and promising clinical activity of CD27 agonists in combination with PD-(L)1 inhibitors. Furthermore, we and others have found that CD27 is one of the most positively differentially expressed genes in tumors treated with MEKi plus PD-L1 (Ebert *et al.*, 2016). This suggests a CD27-targeted therapy may be particularly effective at rescuing T cell activation in the setting of MEKi. The combination of MEK, PD-L1, and CD27 is also supported by preclinical work from other groups showing that MEK inhibition can protect T cells from death from activation-induced cell death (AICD) (Ebert *et al.*, 2016). Chronic overstimulation from constitutive activation of CD27 in mice may result in depletion of the naïve T cells through AICD and may limit the clinical activity of CD27. Thus, MEK inhibition may synergize with CD27 agonism and PD-L1 inhibition by preventing T cell

exhaustion and preventing AICD, while simultaneously reprograming the tumor immune microenvironment through direct effects on tumor antigen presentation and stromal cells. Collectively, the strong translational data when combined the favorable safety profiles and therapeutic signal in BTC supports a study of this triple combination therapy. This trial will be the first in human study to assess the combination of atezolizumab, CDX-1127 (varlilumab) and cobimetinib.

2.4 Correlative Studies Background

2.4.1 CD8+ effector cells

Integrated biomarker assessed with IHC using Cell Marque, CD8 (C8/144B) mouse monoclonal antibody (Ref#108M-98, status IVD, Validated for CTEP by study collaborator Dr. Robert Anders.

Our primary correlative objective will be to compare infiltration of CD8+ T cells into the tumor microenvironment between patients receiving atezolizumab and variliumab and those receiving this same combination with concurrent cobimetinib. This validated metric will be considered an integrated biomarker for the clinical study.

It has been demonstrated in various malignancies that the presence of CD8+ effector T cells within tumors increases the likelihood of responding to PD-1/PD-L1 antibody blockade (ICB) (Chen *et al.*, 2020; Maibach *et al.*, 2020).

This correlative objective has two distinct hypotheses. First, we hypothesize the combination of atezolizumab and variliumab will increase the total number of CD8+ T effector cells and lead to an increased intratumoral ratio of CD8+ T effector cells CD4+FoxP3+ T regulatory cells. We postulate this effect will be further augmented in patients receiving concurrent cobimetinib. Second, we hypothesize that greater treatment-related changes in CD8+ T cell infiltration will occur in biliary tract tumors and that increased CD8+ T cell infiltration will correlate with a favorable clinical response to therapy.

2.4.2 PD-L1 expression

Exploratory biomarker assessed with IHC using SP142 [Spring, Biosciences] in collaboration with Dr. Robert Anders.

Across tumors of multiple histologic type, PD-L1 expression measured by immunohistochemistry (IHC) is a well-characterized biomarker for predicting patient response with PD-1/PD-L1 blockade (Patel & Kurzrock, 2015). However, the utility of this biomarker in biliary tract cancers in the context of combination immunotherapy, and the effect of MEK inhibition on PD-L1 expression, are unknown. In theory, upregulation of PD-L1 may reflect a tumor with potential for immune reactivity, as various T cell derived cytokines (i.e. interferon-gamma) are well-characterized positive regulators of PD-L1 expression. We will use a previously validated technique and assay to assess this exploratory biomarker (Mody *et al.*, 2016; Rimm *et al.*, 2017)

We hypothesize that patients with increased expression of PD-L1 at baseline will be more likely to respond to therapy regardless of treatment arm.

We hypothesize that treatment with atezolizumab and CDX-1127 (varlilumab) will increase PD-L1 expression and TILs as compared to each patient's baseline, and that addition of cobimetinib to this combination will induce further increase in both PD-L1 and TIL in patient tumors.

2.4.3 Tumor Microenvironment (TME) Assessment

Panel of exploratory biomarkers assessed multiplex IHC and RNA seq [Johns Hopkins Core Lab Platforms] to characterize TME and immune subsets

Both novel therapeutic combinations being tested in this clinical trial have the potential increase the potency of on-site anti-tumor immune response through direct action on TILs and/or indirect modulation of the TME. This trial provides a unique opportunity to conduct exploratory analysis to assess quantitative and qualitative changes in the TME and specifically the effects on immune cell subsets. This will be assessed with a broad panel of exploratory biomarkers through multiplex IHC for purposes of hypothesis-generating studies.

We hypothesize the combination of cobimetinib, CDX-1127 (varlilumab), and atezolizumab will result in increased activated effector T cell, decreased regulatory T-cells, increased MHC-I expressions, as well decreased expression of inhibitor receptors and exhaustion markers as compared to baseline or doublet therapy.

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 (obtained cycle 1 day 21 [+/- 5days]) 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 and varilulumab +/- cobimetinib.

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. At time of tissue analysis, the final components of this exploratory TME panel may be updated based on scientific and biomarker advances that have taken place since writing of original study protocol.

We will explore changes in the TME using a multispectral IHC platform co-developed by investigators at Johns Hopkins University that incorporates a computational image processing workflow. This approach enables simultaneous evaluation of 12 biomarkers on one FFPE section and co-localization of multiple markers for highly specific immune cell phenotyping and has previously been used to characterize the tumor microenvironment (Romero *et al.*, 2018). This

work will be conducted in collaboration with a liver pathologist and immunologist, Dr. Robert Anders.

Table 1 - Example Immunohistochemical (IHC) and Immunofluorescence (IF) analysis

IHC Stains**	**IF Stains****	
CD8* PD-L1 CD4 MHC-I	CD8+Ki67+ CD4+FoxP3+	**Priority 1**
CD11c CD19 CD38 CD68 CD69 CD163 PD1 IDO1 LAG3	CD33+S100+ CD4+IL-17+	**Priority 2**
*Denotes integrated biomarker **At time of tissue analysis, the final components of the exploratory IHC/IF panel may be updated based on scientific and biomarker advances that have taken place since writing of original study protocol		

2.4.4 Atezolizumab and CDX-1127 (varlilumab) clearance as an early marker of response and survival

Antibody drug clearance has demonstrated potential as an early biomarker for outcomes from immune checkpoint inhibitor therapy (Desnoyer *et al.*, 2020; Mir *et al.*, 2020). In particular, baseline clearance (CL0, the clearance of the first dose of antibody drug) and/or changes in clearance over time have been demonstrated to associate with progression-free and/or overall survival for CTLA-4-targeted (Sanghavi *et al.*, 2019), PD1-targeted (Baverel *et al.*, 2018; Coss *et al.*, 2018; Food and Drug Administration, 2016b; Turner *et al.*, 2018; Zheng *et al.*, 2018), and PD-L1-targeted agents (Baverel *et al.*, 2018; Wilkins *et al.*, 2019), including atezolizumab (Food and Drug Administration, 2016a) (low baseline clearance and decreasing clearance over time correlates with better outcomes).

Elevated baseline clearance is also observed in patients with cancer-associated cachexia, and decreasing clearance over time trends with weight gain in patients who are responding to therapy (Turner *et al.*, 2018; Patel *et al*., 2016;, Roch *et al*., 2020; Shek *et al*., 2020; Li *et al*., 2017).

We hypothesize baseline clearance of atezolizumab will correlate with progression-free survival (lower baseline clearance will be associated with longer PFS). Atezolizumab and CDX-1127 (varlilumab) blood levels will be measured by two separate ELISAs (one for each drug) in blood serum pre-dose and within 30 minutes after the end-of-infusion. The drug clearance for atezolizumab and CDX-1127 (varlilumab) will be assessed. We will also assess the correlations

between atezolizumab and CDX-1127 (varlilumab) clearance at baseline and over time, as well as associations between cachexia and antibody drug clearance. Finally, we will assess immunogenicity by testing for the presence of anti-drug antibodies (ADAs) to both atezolizumab and CDX-1127 (varlilumab) using screening ELISAs followed by bridging ELISAs for positive samples.

2.4.5 Circulating immune markers in peripheral blood (Th/Tc, phenotype, naïve/memory and exhaustion markers [PD-1, CTLA4, ICOS, BTLA, LAG3, TIM-3]) and plasma cytokines (Th1/Th2/Th17).

Administration of the immunomodulatory agents included in this clinical trial has potential to elicit potent systemic shifts in cytokines that occur downstream of T cell activation. Each therapeutic antibody included in the regimen has potential to induce immune cell activation. Similarly, MEKi may be particularly adept at modulating cytokine secretion from tumor or stromal cells that lead to local or systemic shifts in Th1, Th2 and Th17 profiles.

Since, in many cases of BTC, it is difficult to obtain enough biopsy tissue to reflect all tumor heterogeneity and to properly study TIL phenotype and location in situ. Thus, increasing studies have focused on studying the profile of blood circulating immune cells to predict the immunotherapy response.

This trial provides a unique opportunity to conduct exploratory analysis to assess quantitative and qualitative changes in peripheral T-cell response and evaluate T-cell quality by characterizing cellular markers associated with poly–functionality, exhaustion, memory, and activation. The interactions between CD27 agonism and PD-L1 and/or MEK inhibition on systemic immune biomarkers have not been carefully examined and will provide a comprehensive dataset that can be integrated with clinical outcome measures including survival, response, or toxicity (Sanjabi & Lear, 2021)

We hypothesize a greater frequency of circulating T cells with memory phenotype will be evident in patients receiving cobimetinib in combination with atezolizumab and CDX-1127 (varlilumab) as compared to patients treated with atezolizumab and CDX-1127 (varlilumab) alone. In addition, we predict that patients who respond to treatment will have fewer inhibitory checkpoint receptors concurrently expressed on their circulating CD4+ or CD8+ T cells and a lower frequency of circulating cytokines or cells that are associated with an IL-17-driven immune responses.

2.4.6 ctDNA

Molecular profiling of advanced cancer is increasingly clinically relevant in terms of tailor targeted therapies and identifying prognostic marker. The clinical utility of circulating tumor DNA (ctDNA)for patients diagnosed with advanced BTC (especially iCCA) is widely accepted (Lamarca et al., 2020). BTCs have the greatest number of actionable molecular abnormalities among GI cancers (Marin et al., 2020), including ~15% with FGFR2 rearrangements/fusions (FDA-approved FGFRi (Bekaii-Saab et al., 2020)), 20-25% with IDH1 mutations (ivosidenib with a survival benefit (Abou-Alfa et al., 2020)) and 3-5 % with Her2 amplifications (response

rate >30% with Her2 directed therapy (Javle et al., 2017)).

FoundationOne Liquid CDx is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, rearrangements in four (4) genes and copy number alterations in three (3) genes (Foundations Medicine, 2021). It is already approved for use as a companion diagnostic tool in advanced NSCLC, Prostate, Ovarian, and Breast Cancers (Foundations Medicine, 2021; Food and Drug Administration, 2020)

The emergence of ctDNA analysis represents a vital tool in the diagnosis and management of BTC patients given the standard tissue biopsy samples are often inadequate for molecular profiling. From a treatment perspective, in addition to identifying actionable mutations with a growing list of targeted therapies in this tumor space, ctDNA can be used for monitoring response to therapy. Accordingly, plasma sampling for ctDNA to assess for the status of these mutations has become standard of care (SOC) for BTC patients at baseline, and is reimbursed by insurance in normal practice.

Several studies have demonstrated high concordance between tissue and commercial ctDNA assays in BTC patients (Aguado et al., 2020; Ettrich et al., 2019; Lamarca et al., 2020; Mody et al., 2019). Gatekeeper mutations have been identified that result in resistance to molecularly targeted therapies, discovered by serial and post-progression liquid biopsies (Goyal et al., 2017; Parikh et al., 2019; Parikh et al., 2020). Beyond diagnostics and precision medicine guidance, the use of high tumor mutation burden (hTMB, ≤10 mut/mb) as a biomarker in BTC, specifically as predictor of response to immunotherapies, is any area of particular clinical relevance to this study of novel immunotherapy combination regimens. A recently published study by Zhang and colleagues reported three BTC cases (one iCCA and two dCCAs) with TMB-H, which were treated with ICIs with two achieving partial responses (PRs) and one patient achieving a complete response (CR) (Zhang et al., 2020)

In this study, we will use ctDNA to explore circulating tumor genomic characteristics (e.g. TMB) as biomarkers for response and resistance to therapy.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Pathologically confirmed biliary tract cancer, 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 perioperative therapy/day of surgery [whichever is more recent] 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 by RECIST v1.1

3.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of atezolizumab, cobimetinib, and CDX-1127 (varlilumab) 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 Patients must have adequate organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– hemoglobin	≥ 9.0 g/dl
– platelets	≥100,000/mcL
– total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN) (Patients with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)
– AST(SGOT)/ALT(SGPT)	≤ 3 × institutional ULN
– Serum creatinine	≤ 1.5 x institutional ULN OR
– creatinine clearance	>30 mL/min/1.73 m2 (calculated by Cockcroft-Gault method) for patients with creatinine levels above institutional normal
– albumin	≥ 3.0 g/dL
– PT/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)
- CK/CPK	< 5 x ULN
– Oxygen saturation	≥ 92% on room air
– Left Ventricular Ejection Fraction	> 50%

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

3.1.7 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.8 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.9 Patients must be willing to undergo 2 sets of core needle biopsies. If possible, biopsied sites should be different than those used for measurable disease/RECIST measurements, but this is not mandatory.

3.1.10 Patients must have an estimated life expectancy of greater than 3 months.

3.1.11 Patients must be able to swallow pills

3.1.12 Patients should not have evidence of retinal pathology on ophthalmologic examination; or neurosensory retinal detachment, RVO, or neovascular macular degeneration.

3.1.13 The effects of atezolizumab, cobimetinib, and CDX-1127 (varlilumab) on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 5 months after the last dose of Atezolizumab. 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. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 5 months (150 days) after completion of atezolizumab, cobimetinib, and CDX-1127 (varlilumab) administration.

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

3.2 Exclusion Criteria

3.2.1 Patients with prior allogeneic bone marrow transplantation within the past 5 years or prior solid organ transplantation at any point.

3.2.2 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events (other than alopecia or neuropathy) due to agents administered more than 4 weeks earlier. However, the following therapies are allowed:

- Hormone-replacement therapy or oral contraceptives
- Herbal therapy >1 week prior to Randomization (herbal therapy intended as

anticancer therapy must be discontinued at least 1 week prior to Randomization)
- Palliative radiotherapy for bone metastases >2 weeks prior to Randomization

3.2.3 Prior treatment with anti-CTLA-4, anti-PD-1, or anti-PD-L1 or other immune checkpoint inhibitor therapeutic antibodies or pathway-targeting agents with the following exceptions:
- Patients who have only received previous durvalumab (anti-PD-L1) as part of first line in combination with gemcitabine and cisplatin (TOPAZ-1 regimen [NCT03875235]) **are eligible**.
- Patients who have only received previous pembrolizumab (anti-PD-1) as part of first line in combination with gemcitabine and cisplatin (KEYNOTE-966 regimen [NCT04003636]) **are eligible**.

3.2.4 Prior treatment with MEK or ERK inhibitors

3.2.5 Treatment with any other investigational agent within 4 weeks prior to Randomization.

3.2.6 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-α or interleukin [IL]-2) within 6 weeks prior to Randomization.

3.2.7 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone (>10mg), cyclophosphamide, tacrolimus, sirolimus, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Randomization.
- 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 physiologic doses of systemic corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- The use of topical and inhaled corticosteroids are allowed due to low systemic absorption.

3.2.8 Patients taking bisphosphonate therapy for symptomatic hypercalcemia. Use of bisphosphonate therapy for other reasons (*e.g.*, bone metastasis or osteoporosis) is allowed.

3.2.9 Presence of therapeutically actionable mutation with approved targeted therapy (e.g. FGFR fusion patients are eligible for study therapy in the 3rd line setting). Patient must have received somatic mutation testing (tissue or liquid) prior to enrollment.

3.2.10 Clinically significant ascites (palpable on exam, paracentesis in last 3 months, and/or symptomatic).

3.2.11 Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases are excluded, with the following exceptions:
- Patients with <u>asymptomatic treated CNS metastases</u> may be enrolled, provided <u>all</u>

the criteria listed above are met as well as the following:

- Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
- No stereotactic radiation or whole-brain radiation within 28 days prior to Randomization
- Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids
- Follow-up brain imaging 3 months after central nervous system (CNS)-directed therapy shows no evidence of progression

3.2.12 History of malignant bowel obstruction.

3.2.13 History of severe allergic, anaphylactic, or other hypersensitivity reactions to Chinese hamster ovary cell products, chimeric, humanized, or other recombinant human antibodies or fusion proteins

3.2.14 History of allergic reactions attributed to compounds of similar chemical or biologic composition to atezolizumab, cobimetinib, or CDX-1127 (varlilumab).

3.2.15 Patients receiving any medications or substances that are considered moderate to strong inhibitors or inducers of CYP3A and are not able to switch to an alternative that minimizes interaction potential will ineligible. Coadministration of cobimetinib with a strong CYP3A4 inhibitor can increase cobimetinib systemic exposure significantly (e.g. itraconazole increased serum systemic cobimetinib exposure by 6.7 fold). On the other end, coadministration of cobimetinib with a strong CYP3A inducer may decrease cobimetinib systemic exposure by more than 80% thus reducing its efficacy. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; 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. Appendix C should be presented to patient.

- Patients on mild inhibitors or inducers of CYP3A are allowed.

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

3.2.17 Patients who have received immunosuppressive treatment for systemic 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, multiple sclerosis, vasculitis, or glomerulonephritis within the last 2 years.

- Patients with a history autoimmune endocrine disorders on stable doses of physiologic hormone replacement may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (*e.g.*, patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (*e.g.*, hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)
    - Patients with history Guillain-Barré syndrome or myasthenia gravis at any point will not be eligible.

3.2.18 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) <u>is permitted</u>.

3.2.19 Patients with active tuberculosis (TB) are excluded.

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

3.2.21 Signs or symptoms of infection within 2 weeks prior to Randomization.

3.2.22 Received oral or intravenous (IV) antibiotics within 2 weeks prior to Randomization.

3.2.23 Patients receiving prophylactic/suppressive antibiotics will not be eligible.

3.2.24 Major surgical procedure within 28 days prior to Randomization or anticipation of need for a major surgical procedure during the course of the study.

3.2.25 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 Randomization or at any time during the study.

- COVID-19 vaccination is not exclusionary but should be administered at least 7 days before study start.

3.2.26 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.27 Pregnant women are excluded from this study because one or more study agents have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab, cobimetinib, and CDX-1127 (varlilumab), breastfeeding should be discontinued if the mother is treated with atezolizumab, cobimetinib, and CDX-1127 (varlilumab).

3.2.28 Patients who are using ethinyl estradiol containing oral contraceptives when administered concomitantly with cobimetinib, are excluded due to increased risk of venous thromboembolism.

3.2.29 Patients with a history of clinically significant cardiac dysfunction, including the following:

- **Left ventricular ejection fraction (LVEF) below institutional LLN or below 50%, whichever is lower**
- Current unstable angina
- Current symptomatic congestive heart failure (CHF) of New York Heart Association class 2 or higher
- Uncontrolled hypertension ≥Grade 2 (patients with a history hypertension controlled with anti-hypertensives to ≤Grade 1 are eligible).
- Uncontrolled arrhythmias
- Myocardial infarction, severe/unstable angina, symptomatic CHF, cerebrovascular accident or transient ischemic attack within the previous 6 months
- History of treatment with cardiotoxic agents

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for

exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

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 at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,

- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located 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).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an active CTEP status,
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster,
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only), and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff or on a participating roster.To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number 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 number 10476
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration*, and download to complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements For 10476 Site Registration

- A Site Initiation Visit (SIV) is required for each participating site prior to activation. The local site PI must participate on the call as well as their research nurse, study coordinator, and pharmacist. To schedule a SIV, please email the Study Contact and reference the protocol in the subject line of the email.
- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs

registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Special Instructions for Patient Enrollment

Pre-registration Step 0 and Registration Step 1 are to performed at the same time and after patient has completed all elements of the screening and eligibility requirements and is ready to enroll/be randomized.

The Baseline Biopsy is to be conducted after Registration Step 1 is completed and prior to starting the assigned treatment regimen.

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen

Tracking System (STS) unless otherwise noted.

- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link 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 609-619-7862 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. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred) (mandatory) If a block is not available, then submit: • 1 H&E stained slide (4 µm) • 15 unstained, 4 micron, positively charged slides, no cover	Yarchoan Laboratory
Baseline		
	• 3 FFPE tumor tissue blocks (mandatory)[1] • 2 snap frozen tumor cores (mandatory)[1]	Yarchoan Laboratory
	• 8.5 mL peripheral blood in FoundationOne Liquid CDx cfDNA tubes (optional) (see Section 11 [Footnote L])	Foundation Medicine
	• 30 mL peripheral blood in EDTA tubes (mandatory)	Lesinski Laboratory
	• 20 mL in Streck cfDNA tube (mandatory)	EET Biobank
Day 1 of Cycles 1-6, 9 and 12		
• Pre infusion • 30 minutes after the end of infusion of CDX-1127 (varlilumab), which will be administered after atezolizumab	• 6 mL Peripheral blood in red-top tube processed for serum and frozen (mandatory)	OSU Comprehensive Cancer Center (OSUCCC) Pharmacoanalytical Shared Resource (PhASR) Laboratory
Day 15 of Cycles 1 and 2		
• Pre infusion • 30 minutes after the end of infusion of CDX-1127 (varlilumab), which will be	• 6 mL Peripheral blood in red-top tube processed for serum and frozen (mandatory)	OSU Comprehensive Cancer Center (OSUCCC) Pharmacoanalytical Shared Resource (PhASR) Laboratory

administered after atezolizumab)		
Cycle 1 Day 21		
	• 3 FFPE tumor tissue blocks (mandatory)[1] • 2 snap frozen tumor cores (mandatory)[1]	Yarchoan Laboratory
	• 30 mL peripheral blood in EDTA tubes (mandatory)	Lesinski Laboratory
	• 20 mL in Streck cfDNA tube (mandatory)	EET Biobank
Week 12 (End of Cycle 3)		
	• 30 mL peripheral blood in EDTA tubes (mandatory)	Lesinski Laboratory
End of Treatment (EOT)		
	• 30 mL peripheral blood in EDTA tubes (mandatory)	Lesinski Laboratory
	• 20 mL in Streck cfDNA tube (mandatory)	EET Biobank
[1]See Sections 5.2 and 5.5.2 for priority of cores.		

5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

Biopsy #: 1				
Trial Time Point: Baseline				
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	CD8+T effector cells	*≥10%*	FFPE
2	Exploratory	PD-L1 expression on tumor and tumor infiltrating lymphocytes (TILs)	*≥10%*	FFPE

3	Exploratory	Analysis of tumor microenvironment examining changes to focused tumor immune infiltrating lymphocyte populations by multiplex IHC	*≥10%*	FFPE
4-5	Exploratory	Analysis of expression of immune-related pathways in the tumor microenvironment by RNA seq	*≥10%*	Snap Frozen

Biopsy #: 2				
Trial Time Point: Cycle 1, Day 21				
IR Biopsy Definition: Research – No Clinical Impact (All cores from a single biopsy procedure impact research goals, but do not directly impact patient care or benefit the patient.				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	CD8+T effector cells	*≥10%*	FFPE
2	Exploratory	PD-L1 expression on tumor and tumor infiltrating lymphocytes (TILs)	*≥10%*	FFPE
3	Exploratory	Analysis of tumor microenvironment examining changes to focused tumor immune infiltrating lymphocyte populations by multiplex IHC	*≥10%*	FFPE

4-5	Exploratory	Analysis of expression of immune-related pathways in the tumor microenvironment by RNA seq	*≥10%*	Snap Frozen

Note: Pre-biopsy assessments will be reported and tracked through a trial-specific Case Report Form (CRF) within the CTEP Medidata Rave system (see Appendix D).

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

Kits for the collection of **blood in FoundationOne Liquid CDX cfDNA tubes** can be ordered from Foundation Medicine for the ctDNA assay if needed.

Kits for the collection and shipment of **blood in Streck cfDNA tubes** to the EET Biobank can be ordered online via the Kit Management system: https://kits.bpc-apps.nchri.org.

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kits per kit type per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Institutional supplies must be used for all other specimen collection and processing.

5.3.2 Scheduling of Specimen Collections

5.3.2.1 Scheduling of Specimen Collection to the Yarchoan Laboratory

All tissue samples should be sent to the Yarchoan Lab (archival and fresh tumor biopies) on a rolling bases post-processing. Snap frozen cores should be stored in vapor phase liquid nitrogen. If the collecting site does not have liquid nitrogen storage capabilities, fresh frozen tissue should be kept at -80ºC and sent to the Yarchoan laboratory within 5 days of tissue procurement (ship on Monday-Wednesday only). An email notification must be sent to the Yarchoan Laboratory on the date of shipping to the following email addresses: (jleathe3@jhmi.edu, smitch55@jhmi.edu, and ctep10476@lists.johnshopkins.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.

5.3.2.2 Scheduling of Specimen Collection to the Lesinski Laboratory

Whole blood samples (three 10mL EDTA tubes total) should be shipped the same day as

collection and can be stored at ambient temperature until shipped. It is imperative that samples be drawn only Monday – Thursday only and shipped same day to ensure quality of the cells and plasma and avoid problems with weekend/holiday delivery.

On the day that the specimens are to be shipped, notify [redacted] at [redacted] of the pending specimen shipments. Include the Fed-Ex tracking number in the email.

5.3.2.3 Scheduling of Specimen Collection to the OSUCCC PhASR Laboratory

Specimens should be stored through the end of Cycle 12 and shipped as a batch by participant (more than one participant/shipment is acceptable). A participant's samples should be shipped to the OSUCCC PhASR lab within 2 weeks of the last sample's collection date. (i.e., if C12D1 sample is collected on 9/1/2021, all of that participant's samples should be at the OSUCCC PhASR lab by 9/15/2021). The OSUCCC PhASR lab may contact the study team to request shipment off-schedule.

Please ship only 1 aliquot to the OSUCCC PhASR laboratory within each shipment. Once receipt is confirmed, the back-up aliquot(s) may also be shipped. The back-up aliquots can be shipped at a later date with subsequent batches of samples for other participants.

All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state. Overnight shipments should occur on Monday through Wednesday except when the following day is a holiday.

Please notify the OSUCCC PhASR lab by email (PhASR@osumc.edu) within 24 hours prior to shipment.

The OSUCCC PhASR laboratory is equipped with -80°C freezers that are continuously monitored and recorded to ensure freezer integrity and that temperatures stay within specified ranges. If freezers deviate outside of specified ranges, PhASR staff is immediately notified, and any necessary corrective action is initiated. All samples acquired from patients enrolled on this study and that are sent to the OSUCCC PhASR will be stored within these monitored freezer systems prior to and after sample processing and analysis is completed.

5.3.2.4 Scheduling of Specimen Collection to Foundation Medicine

Whole blood samples should be shipped the same day as collection and should be stored at ambient temperature until shipped. Do not freeze or refrigerate the samples. Samples should only be collected monday-thursday.

5.3.2.5 Scheduling of Specimen Collection to the EET Biobank

Fresh blood specimens may be collected and shipped Monday through Friday.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

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

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

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

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

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

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

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

5.4.2 Specimen Labeling

5.4.2.1 Blood Specimen Labels

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

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

5.4.2.2 Tissue Specimen Labels

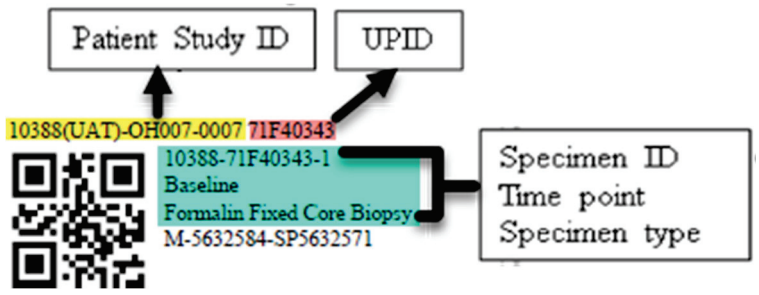
Include the following on all tissue specimens (*e.g.*, FFPE block, or frozen tissue):

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

5.4.2.3 Example of Specimen Label Generated by STS

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

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



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

Labels may be printed on a special purpose label printer, one label at a time, or on a standard

laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

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

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

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

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

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

Registration without eligibility specimen analysis:

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

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

5.4.3.2 Rave Specimen Tracking Process Steps

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

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

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

Specimen ID.

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

- Label specimen containers and write collection date on each label. After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Bone Marrow [*if bone marrow is submitted]*, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or the Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. **Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document** (either by adding a label or hand writing).

Step 3: Complete specimen data entry.

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

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

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

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

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

Step 6: Send email notification.

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

Step 7: Ship the specimen(s).

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

5.5 Specimen Collection

5.5.1 Archival Tumor Tissues

a. 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).
b. 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, 15 unstained sections, cut at 4 micrometers and mounted in poly-l-lysine-coated or plus (+) slides.
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.
d. The following guidelines should be used for preparation of slides:
    i. Slides #1: to be regular 4 microns, positively charged slide, H&E, with cover
    ii. Slides #2 and above: 4 microns, positively charged slides, unstained, NO COVER
    iii. Blades need to be changed between blocks, if more than one block is being cut.
    iv. If possible, slides and process need to be DNAase free and tissue should be mounted on the bottom third of the slide.

5.5.2 Fresh Tumor Specimens

a. Supplies
    i. 10% Neutral Buffered Formalin (ambient/room temperature) (VWR #16004-115)
    ii. Cryovial tubes – 1.8 ml cryotubes/vials (e.g., Nunc Code #377267 or equivalent)
    iii. Conical tubes – 15 mL (e.g., Sarstedt Code #62.554.001 PP or equivalent)
b. 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).
c. A maximum of 5 core biopsies (or fine needle aspirates, if cores are considered unsafe) will be obtained from each subject whose tumor is amenable to undergo a biopsy.
d. The biopsies will be used to prepare paraffin embedded and frozen samples. A total of 5 biopsies is preferred, when possible.
e. The first pass will generally be used for on-site examination of the material, to determine presence and quality of lesional tissue.
f. The remaining biopsy tissue will be paraffin embedded and frozen at each

respective institution.

g. If a limited amount of tumor tissue is obtained, paraffin embedded tissue should be prioritized over frozen tissue.
h. Archived or freshly obtained paraffin embedded formalin fixed (FFPE) or frozen tissues of biopsied specimens are needed for the purposes of:
    i. Pathological examination (for conventional pathology examination, such as H&E stain)
    ii. Examination of immune and inflammatory fibroblast biomarkers via IHC or IF analysis, as appropriate.
    iii. Future analysis of genomic and transcriptome features within the tumor microenvironment.
i. *Samples will be collected in this order:*
    i. Core 1 – Formalin-fixed paraffin-embedded (FFPE)
    ii. Core 2 – FFPE
    iii. Core 3 – Snap Frozen
    iv. Core 4 – FFPE
    v. Core 5+ – Snap Frozen
    vi. *For example, if only 2 cores are obtained, one core should be FFPE and one core should be snap frozen.*
j. Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimens guide
    i. FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor.
    ii. Specimen size requirement is as follows:
        1. Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
        2. Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.
k. Snap Frozen Specimens guide
    i. The biopsy specimen should be placed in a 1.8 ml cryotubes/vials (e.g., Nunc Code #377267 or equivalent)
    ii. Label the cryovial with the timepoint (eg pretreatment or C1D21), and subject's study ID.
    iii. Rapidly cool - the cryovial should be cooled to -70°C (or lower) very rapidly using dry ice, a -80°C freezer, or liquid nitrogen.
    iv. The snap frozen samples should never be thawed.

5.5.3 Blood Collection

5.5.3.1 Collection of Blood in Red Top Tube for Serum Processing

a. Venous whole blood (6 mL) will be collected into pre-labeled serum (red-top; e.g. BD 367815 or 368660) tubes at the time points specified. Collect each PK sample as close as possible to the planned (nominal) time relative to dosing.
b. If a cannula is used, the cannula will be inserted into an arm vein within sufficient time prior to dosing, kept patent with normal saline or heparin solution, and will be removed as instructed by physician or earlier if the subject requests. To avoid

artificial dilution of the PK samples by saline, 1 mL of whole blood will be collected and discarded before each whole blood PK sample is collected.

c. *Processing at the collection site:*
    i. Allow blood to clot upright at room temperature for at least 30 minutes (maximum 60 minutes) prior to processing.
    ii. If the blood is not immediately processed after the clotting period, then tubes should be stored (after the 30-60 minutes of clotting time) at 4°C for no longer than 4 hours.
    iii. Centrifuging for 10 minutes at 1,200 × g at room temperature.
    iv. Using a clean transfer pipette, aliquot serum into the labeled cryovials (~2-3) at an aliquot volume of 1 mL per tube. Labeling should be printed from the ETCTN Specimen Tracking System (label should include at a minimum the Study ID, Patient ID, sample type, sample collection date, exact sample collection time).
    v. Avoid picking up red blood cells when aliquoting by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube.
    vi. Tightly secure the cap of the vials before storage.
    vii. Aliquoting and freezing of serum specimens should be completed within 1 hour of centrifugation.
    viii. Store serum cryovials upright in a specimen box or rack in a -70°C to -90°C or colder freezer. Do not allow specimens to thaw after freezing.

5.5.3.2 Collection of Blood in EDTA Tubes for Shipping Whole Blood

1. Label EDTA tubes according to the instructions in Section 5.4.2.
2. Collect blood in EDTA tube(s) and gently invert tube to mix.
3. Samples must be collected Monday-Thursday and shipped the same day as collection. Samples can be stored at ambient temperature until shipped as indicated in section 5.6.2.1 below
4. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.
5. Upon arrival at the site of processing (Lesinski Laboratory) biospecimen processing for plasma and PBMCs and subsequent storage methods will follow standard guidelines (Fisher *et al.*, 2018).

5.5.3.3 Collection of Blood in FoundationOne Liquid CDx cfDNA tubes

1. Label tubes with the labels supplied in the FoundationOne Liquid CDx kit.
2. Check the blood collection tubes are clear without cloudiness or crystals.
3. Collect 8.5 mL whole blood in the tube. Fill tube completely but prevent backflow to the patient. Collect sample Monday through Thursday only. Collect sample Monday through Thursday only.
4. Immediately mix by gentle inversions 8 to 10 times. One inversion is a complete turn of the wrist 180 degrees and back.

5. Store at room temperature until shipment. Ship same day as collection. Do NOT freeze or refrigerate samples.

5.5.3.4 Collection of Blood in Streck cfDNA tube for shipment to the EET Biobank

1. Label two 10 mL Streck cfDNA tubes according to the instructions in Section 5.4.2.
2. Collect 10 mL of blood into each pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen. If patients may have an indwelling catheter: heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as the first-choice collection method. If a Streck cfDNA tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT is recommended.
3. **After collection, blood in Streck cfDNA tubes should never be refrigerated,** as this will compromise the specimen. Blood collected in Streck cfDNA tubes is stable at room temperature until shipment to the EET Biobank.

5.6 Shipping Specimens from Clinical Site to the EET Biobank

5.6.1 General Shipping Information

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

5.6.1.1 Required Forms for Specimen Submissions:

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

Tissue	Required Forms
Blood in Streck cfDNA tubes	Shipping List

5.6.2 Specimen Shipping Instructions

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.6.2.1 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions in 5.4.2.1 and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. **Note:** If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth. **Do not refrigerate, freeze, or microwave.**

3. Place the SAF-T-TEMP Pak in bottom of insulated chest. **Note:** The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.2 Shipping Address

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

EET Biobank
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions. There is no central Courier account for this study. Sites are responsible for the cost of shipments to the EET Biobank.

5.6.3 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

5.7 Shipping of Specimens from Clinical Site to Other Laboratories

5.7.1 Shipping of Specimens to Yarchoan Laboratory

5.7.1.1 Specimen Shipping Instructions

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

FFPE specimens may be shipped at room temperature along with corresponding frozen cores, or as a batch shipment.

Each tumor sample must be clearly labelled with the study number (10476) 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.

5.7.1.2 Shipping address for TISSUE BIOPSIES (NOT RESEARCH BLOODS) follows:

Yarchoan Laboratory
Attn: [redacted], NCI 10476
1550 Orleans Street
CRBI Room [redacted]
Baltimore, MD 21287
Tel: [redacted]

5.7.1.3 Contact Information for Assistance

[redacted]
ctep10476@lists.johnshopkins.edu

5.7.2 Shipping of Specimens to Lesinski Laboratory

5.7.2.1 Specimen Shipping Instructions

Three 10 mL purple top tubes of blood containing EDTA as an anti-coagulant will be obtained for correlative studies at each of the pre-specified time points.

Adherent labels will be placed on each tube and using an ethanol-resistant permanent marker label EDTA tubes according to the instruction in Section 5.4.2.
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 stryofoam 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.

5.7.2.2 Shipping Address for RESEARCH BLOODS (NOT TISSUE BIOPSIES) follows:

Lesinski Laboratory
Suite C3054, Bay 17
1365-C Clifton Rd. NE
Winship Cancer Institute of Emory University
Atlanta, GA 30322

5.7.2.3 Contact Information for Assistance

On the day that the specimens are to be shipped, email EMORYCTEP10476@listserv.cc.emory.edu and cc [redacted] and Dr. [redacted] of the pending specimen shipments. Include the Fed-Ex tracking number in the email.

Research blood contact information:
[redacted], Ph.D., MPH [redacted]

5.7.3 Shipping of Specimens to OSUCCC PhASR Laboratory (Blood Samples for Drug Clearance and Immunogenicity Studies only)

5.7.3.1 Specimen Shipping Instructions

Specimens should be stored through the end of Cycle 12 or End of Treatment (whichever comes first) and shipped as a batch by participant (more than one participant/shipment is acceptable).

A participant's samples should be shipped to the OSUCCC PhASR lab within 2 weeks of the last sample's collection date. (i.e., if C12D1 sample is collected on 9/1/2021, all of that participant's samples should be at the OSUCCC PhASR lab by 9/15/2021).

The OSUCCC PhASR lab may contact the study team to request shipment off-schedule.

Please ship only 1 aliquot to the OSUCCC PhASR laboratory within each shipment. Once receipt is confirmed, the back-up aliquot(s) may also be shipped. The back-up aliquots can be shipped at a later date with subsequent batches of samples for other participants.

Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH) with dividers. (e.g., VWR Box item number is 82021-114; divider item number is 82007-154.)

Please organize the samples by Patient and Time point in the box.

Do not store in plastic bags (they break on dry-ice and labels will detach).

A copy of each of the pharmacokinetic sample collection forms for the respective patients or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.

Note the study number, PI, and the drugs used/to be measured (i.e. atezolizumab and CDX-1127 (varlilumab).

A name, phone number and email address should be included with samples so that receipt can be acknowledged.

All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.

Overnight shipments should occur on Monday through Wednesday except when the following day is a holiday.

Please notify the OSUCCC PhASR lab by email (PhASR@osumc.edu) within 24 hours prior to shipment.

5.7.3.2 Shipping Address

The OSUCCC Pharmacoanalytical Shared Resource
Attn: [redacted], Ph.D.
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, OH 43210
Phone: [redacted]

5.7.3.3 Contact Information for Assistance

OSUCCC PhASR lab

PhASR@osumc.edu
[redacted], PhD or [redacted], PhD can be reached at: ([redacted]
[redacted], PhD can be reached at: ([redacted]

5.7.4 Shipping of Specimens to Foundation Medicine (Blood Samples for ctDNA Studies only)

5.7.4.1 Specimen Shipping Instructions

Package and mail the specimen(s) to the Foundation Medicine laboratory. Each kit should be utilized for one patient. Do not include different patient samples in the same box.

Shipping Instructions

1. Remove the kit tracking information and keep for your records.
2. Place the specimen kit (including samples and paperwork) into the provided FedEx shipping pack, first ensuring that primary specimen containers (e.g. tubes) are labeled with two patient-specific identifiers. Seal the shipping pack.
3. If using shipping pack provided in this kit (recommended), recording the Kit ID # will allow you to properly track specimen. If you use a different shipping pack, consider recording that pack's tracking number.
4. Call 800.463.3339 to request a pick-up or drop the package at your site's designated FedEx pick-up location and ship sealed shipping pack.

5.7.4.2 Shipping Address

Foundation Medicine, Inc.
150 Second Street
Cambridge, MA 02141

5.7.4.3 Contact Information for Assistance

Phone: 888.988.3639

5.8 Biomarker Plan

List of Biomarker Assays in Order of Priority

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the laboratory prior to testing.

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	CD8+T effector cells	IHC CLIA: N	Integrated To determine the effect of combination atezolizumab and CDX-1127 (varlilumab) +/- cobimetinib on CD8+ effector tumor infiltrating lymphocytes population	FFPE Tumor tissue	Archival, Baseline and C1D21	M	Assay (Validated by [redacted]) Yarchoan Laboratory, Johns Hopkins School of Medicine [redacted] Johns Hopkins University School of Medicine [redacted]
2	Tumor PD-L1 expression	IHC CLIA: N	Exploratory To explore changes in the tumor microenvironment that may impact response to therapy	FFPE Tumor Tissue	Archival, Baseline and C1D21	M	Assay (Validated by [redacted]) Yarchoan Laboratory, Johns Hopkins School of Medicine [redacted] Johns Hopkins University School of Medicine [redacted]

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
3	Analysis of tumor microenvironment (TME)	Multiplex IHC CLIA: N	Exploratory To explore the effect of combination CDX-1127 (varlilumab), and atezolizumab +/- cobimetinib on the tumor microenvironment examining changes to tumor immune infiltrating lymphocyte populations (TILs) and correlate these trends with therapeutic response	FFPE Tumor tissue	Archival, Baseline and C1D21	M	Yarchoan Laboratory, Johns Hopkins School of Medicine [redacted]
4	Analysis of expression of immune-related pathways in the tumor microenvironment (TME)	RNA Seq CLIA: N	Exploratory To explore the effect of combination CDX-1127 (varlilumab), and atezolizumab +/- cobimetinib on the tumor microenvironment examining changes to expression of immune-related pathways and correlate these trends with therapeutic response	Snap Frozen	Archival, Baseline and C1D21	M	Yarchoan Laboratory, Johns Hopkins School of Medicine [redacted]

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Blood-based Biomarkers							
1	Atezolizumab and CDX-1127 (varlilumab) clearance Immunogenicity, anti-drug antibodies (ADAs) for atezolizumab and CDX-1127 (varlilumab)	ELISA for CDX-1127 (varlilumab) PK CLIA: N but GLP and ELISA for atezolizumab PK CLIA: N but GLP	Integrated PK samples are to explore baseline and time-varying clearance of atezolizumab and CDX-1127 (varlilumab) as potential biomarkers for response therapy. The same samples will also be used to identify immunogenicity and presence of ADA for both atezolizumab and CDX-1127 (varlilumab)	Serum from peripheral blood in red top tubes	Day 1 of Cycles 1-6, 9 and 12 Pretreatment and 30 minutes after the end of infusion of CDX-1127 (varlilumab), which will be administered after atezolizumab Day 15 of Cycles 1-2: Pretreatment and 30 minutes after the end of infusion of CDX-1127 (varlilumab), which will be administered after atezolizumab	M	Pharmacoanalytic at Shared Resource (PhASR), Ohio State University (OSU) Comprehensive Cancer Center [redacted]
2	ctDNA	NGS CLIA: Y	Integrated To explore how circulating tumor genomic characteristics (e.g. tumor mutation burden) may serve	DNA from Peripheral blood in Foundation One Liquid CDx cfDNA tubes	Baseline	O	Foundation Medicine

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
			as biomarkers for response and/or resistance to study therapies.				
3	Circulating T cell phenotypic and functional markers in peripheral blood (Th/Tc, phenotype, naïve/memory and exhaustion markers	Mass Cytometry CLIA: N	Exploratory To explore the effect of dual anti-combination CDX-1127 (varlilumab), and atezolizumab +/- cobimetinib on T cell immune regulatory markers, and their impact on response to therapy.	PBMCs from Peripheral blood in EDTA tubes	Baseline, C1D21, and Week 12 (end of Cycle 3), EOT	M	Lesinski Laboratory, Winship Cancer Institute of Emory University [redacted] Paulos Laboratory, Winship Cancer Institute of Emory University [redacted]
4	Circulating Plasma Cytokines (Th1/Th2/Th17 cytokine profiles)	Luminex, ELISA CLIA: N	Exploratory To explore the effect of CDX-1127 (varlilumab), and atezolizumab +/- cobimetinib on systemic cytokine biomarkers, their relationship to Th-profile and impact on response therapy.	Plasma from Peripheral blood in EDTA tubes	Baseline, C1D21, and Week 12 (end of Cycle 3), EOT	M	Lesinski Laboratory, Winship Cancer Institute of Emory University [redacted] Paulos Laboratory, Winship Cancer Institute of Emory University [redacted]

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
5	Circulating Tumor DNA (ctDNA)	TSO500 CLIA: N	Exploratory To assess concordance between the tissue and liquid biopsies; to capture a comprehensive mutational profile; and to explore how circulating tumore genomic characteristic may serve as biomarkers for response and/or resistance to study therapies.	Plasma from blood in Streck cfDNA tube	Baseline, C1D21, and EOT	M	NCLN Genomics or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) [redacted]

5.9 Integrated Correlative Studies

5.9.1 CD8+T effector cells

5.9.1.1 Specimen Receipt and Processing Yarchoan Laboratory, Johns Hopkins School of Medicine

FFPE blocks will be received and stored as appropriate until analysis.

5.9.1.2 Site(s) Performing Correlative Study

Yarchoan Laboratory, Johns Hopkins School of Medicine

5.9.1.3 Contact information for notification of specimen shipment

See Section 5.6.1

5.9.2 Atezolizumab and CDX-1127 (varlilumab) clearance and ADA

5.9.2.1 Specimen Receipt and Processing at PhASR, Ohio State University

Aliquots of serum will be received and stored until the time of analysis. Sample analysis for PK will be completed using two validated ELISA assays, one each for CDX-1127 (varlilumab) and atezolizumab. Using drug concentration *vs.* time data through Cycle 6 and nonlinear mixed effects modeling, we will estimate the baseline and time-varying clearance for each of the two drugs. For immunogenicity assessment, two separate ADA screening ELISAs will be used, one each for CDX-1127 (varlilumab) and atezolizumab. Samples yielding positive results will be subsequently tested in bridging ELISAs, one each for CDX-1127 (varlilumab) and atezolizumab, for confirmation of ADA.

5.9.2.2 Site(s) Performing Correlative Study

PhASR, Ohio State University

5.9.2.3 Contact information for notification of specimen shipment

See Section 5.6.3.

5.9.3 ctDNA

5.9.3.1 Specimen Receipt and Processing Foundation Medicine

Whole blood will be received and processed to plasma. The DNA will then be isolated from the plasma and analyzed (https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032B.pdf).

5.9.3.2 Site(s) Performing Correlative Study

Foundation Medicine per standard of care.

5.9.3.3 Contact information for notification of specimen shipment

See Section 5.6.4.

5.10 Exploratory/Ancillary Correlative Studies

5.10.1 Tumor PD-L1 expression

5.10.1.1 Specimen Receipt and Processing Yarchoan Laboratory, Johns Hopkins School of Medicine

FFPE blocks will be received and stored as appropriate until analysis.

5.10.1.2 Site(s) Performing Correlative Study

Yarchoan Laboratory, Johns Hopkins School of Medicine

5.10.1.3 Contact information for notification of specimen shipment

See Section 5.6.1

5.10.2 Tumor Microenvironment (TME) Assessment - Tumor infiltrating lymphocyte and immune pathway analysis

5.10.2.1 Specimen Receipt and Processing Yarchoan Laboratory, Johns Hopkins School of Medicine

FFPE blocks and frozen tumor cores will be received and stored as appropriate until analysis.

5.10.2.2 Site(s) Performing Correlative Study

Yarchoan Laboratory, Johns Hopkins School of Medicine.

5.10.2.3 Contact information for notification of specimen shipment

See Section 5.6.1

5.10.3 Circulating T cell phenotypic and functional markers in peripheral blood (Th/Tc, phenotype, naïve/memory and exhaustion markers [e.g. PD-1, CTLA4, ICOS, BTLA, LAG3, TIM, etc.,.])

5.10.3.1 Specimen Receipt and Processing Lesinski Laboratory, Winship Cancer Institute of Emory University

Blood in EDTA tubes will be received, processed for PBMCs, and stored frozen until analysis.

5.10.3.2 Site(s) Performing Correlative Study

Lesinski Laboratory, Winship Cancer Institute of Emory University and Paulos Laboratory, Winship Cancer Institute of Emory University

5.10.3.3 Contact information for notification of specimen shipment

See Section 5.6.2.

5.10.4 Circulating Plasma Cytokines (Th1/Th2/TH17 cytokine profiles)

5.10.4.1 Specimen Receipt and Processing Lesinski Laboratory, Winship Cancer Institute of Emory University

Blood in EDTA tubes will be received, processed to plasma, and stored frozen until analysis.

5.10.4.2 Site(s) Performing Correlative Study

Lesinski Laboratory, Winship Cancer Institute of Emory University and Paulos Laboratory, Winship Cancer Institute of Emory University

5.10.4.3 Contact information for notification of specimen shipment

See Section 5.6.2.

5.10.5 ctDNA Sequencing

5.10.5.1 Specimen(s) Receipt and Processing at the EET Biobank

Whole blood collected in Streck cfDNA tubes will be processed for plasma and buffy coat. Plasma and buffy coat aliquots will be stored in a -80°C freezer.

5.10.5.2 Site(s) Performing Correlative Study

ctDNA sequencing will be performed at the NCLN Genomics Laboratory or the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Dr. [redacted]

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

Specimens will be shipped from the EET Biobank to one of the laboratories designated in

Section 5.10.5.2.

5.10.5.4 Contact Information for Notification of Specimen Shipment

[redacted] (NCLNGenomicsReceiving@nih.gov)

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. For all patients, atezolizumab is administered first, followed by CDX-1127 (varlilumab). For patients on Arm A and on infusion days, cobimetinib is to be taken prior to starting atezolizumab. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description -Arm A					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule****	**Cycle Length**
Atezolizumab	Premeds are not permitted for the first infusion. If patient experiences an Infusion-Related Reaction (IRR), pre-medication with antihistamines may be administered for subsequent infusions at the discretion of the treating physician.	840 mg	IV (Initial dose delivered over approximately 60 minutes. Subsequent infusions may be delivered over approximately 30 minutes if initial infusion is tolerated without infusion-associated AEs.	Days 1 and 15	28 days (4 weeks)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

	[redacted]				
Cobimetinib	Cobimetinib should be taken at the same time every morning. It can be taken with or without food*.	60 mg	PO	Daily, Days 1-21	

* The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course (Appendix E). If patient misses a day, they should resume their normal dose/time the next day and not "make up" the missed dose. If patient is unable to take their dose within 4 hours of regularly scheduled time on the same day, that day's dose should be considered missed and not taken. Resume dosing at the next scheduled dose/time.

**On Days 1 and 15, Cobimetinib should be taken before arrival for infusion of Atezolizumab & CDX-1127 (varlilumab). Atezolizumab infusion should be administered first followed by CDX-1127 (varlilumab). Required wait time of 30 minutes between completion of atezolizumab and subsequent start of CDX-1127 (varlilumab). If unable to take dose prior to infusion, patient may still take that day's dose as long as it is within 4 hours of regularly scheduled morning time, otherwise it should be considered missed and not taken. Resume dosing at the next scheduled dose/time.

Regimen Description -Arm B					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule****	**Cycle Length**
Atezolizumab	Premeds are not permitted for the first infusion. If patient experiences an Infusion-Related Reaction (IRR), pre-medication with antihistamines may be administered for subsequent infusions at the	840 mg	IV (initial dose over approximately 60 minutes. Subsequent infusions may be delivered over approximately 30 minutes if initial infusion is tolerated without infusion-	Days 1 and 15	28 days (4 weeks)

	discretion of the treating physician.		associated AEs.		
					
**Atezolizumab should be administered first followed by CDX-1127 (varlilumab). Required wait time of 30 minutes between completion of atezolizumab and subsequent start of CDX-1127 (varlilumab).					

6.1.1 CTEP IND Agents

6.1.1.1 Atezolizumab

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

Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) will be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • Vital signs will be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients will be observed for at least 4	• If the patient experienced an infusion–related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs will be measured within 60 minutes prior to the infusion, within 30 minutes after the infusion, and as clinically indicated during the infusion. • Atezolizumab should be infused over

hours after the completion of all infusions. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion–related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be observed for at least 1 hour after the last study drug infusion.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

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

Procedures

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

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

6.1.1.2 CDX-1127 (varlilumab)

CDX-1127 (varlilumab) will be given on Day 1 and Day 15 of each 28 day cycle at a dose of 3 mg/kg. Baseline weight may be used for calculating the dose each cycle. The dose will be recalculated when weight changes by ± 10%.

Required wait time of 30 minutes between completion of atezolizumab and subsequent start of CDX-1127.

All patients will be monitored for at least 4 hours following the completion of all infusions on the first dose (i.e. Day 1 of Cycle 1) and at least 1 hour following all subsequent doses. Vital sign measurements should be done similar as is stated for atezolizumab (section 6.1.1.1).

CDX-1127 (varlilumab) cannot be mixed with any other drug in the infusion bag or the administration set.

6.1.1.3 Cobimetinib

Patients will receive cobimetinib at a dose of 60 mg (three tablets of 20 mg each) orally once daily 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 7.

Cobimetinib should be taken in the morning at the same time every day. It can be taken with or without food. If a dose of cobimetinib is not taken within 4 hours of the scheduled dose, it should be considered missed and not taken. Resume dosing at the next scheduled dose. If vomiting occurs when the dose is taken, resume dosing with the next scheduled dose.

Patients receiving cobimetinib will be requested to maintain a medication diary (see Appendix 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.

6.1.1.4 Pregnancy

All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation and 5 months after the last dose of Atezolizumab or 3 months after the last dose of cobimetinib.

6.2 Continuation after Unconfirmed Progression

The study regimens in this trial trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Patients may continue receiving their assigned treatment if their disease progresses based on RECIST 1.1 criteria if 1) the patient is clinically stable; 2) No symptoms or signs indicating disease progression, including clinically significant laboratory values; 3) the patient is informed of their scan results and agrees to continue therapy, and 4) the patient provider agrees that remaining on study would be appropriate for the patient. If the following scan after first noted progression confirms progressive disease by RECIST 1.1, the scan where progression was first note will be used to calculate PFS.

6.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of atezolizumab, cobimetinib, and CDX-1127 (varlilumab) 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. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Clinical Trial Wallet Card) should be provided to patients if available.

6.3.1 Atezolizumab General Concomitant Medication Guidelines

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).

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 ≥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 or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

6.3.2 Atezolizumab Excluded Therapies

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 6.2.1**).
    - After Cycle 1, certain forms of radiotherapy may be considered for pain palliation

if patients are deriving benefit (*e.g.*, treatment of known bony metastases); atezolizumab administration may be suspended during radiotherapy.

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.

6.3.3 [redacted]

[redacted]

6.3.4 Cobimetinib

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. Use an alternative to a strong or moderate CYP3A inhibitor in patients who are taking a reduced dose of cobimetinib (40 or 20 mg daily). If concurrent short term (14 days or less) use of moderate CYP3A inhibitors is unavoidable for patients who are taking cobimetinib 60 mg, the dose of cobimetinib may be reduced to 20 mg and the previous dose of cobimetinib 60 mg can be resumed following moderate CYP3A inhibitor discontinuation. See Section 8 for further information. Concomitant administration of cobimetinib with oral contraceptives containing ethinyl estradiol is prohibited due to increased risk of venous thromboembolism.

6.4 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
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity [adverse event(s)]
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation and 5 months after the last dose of Atezolizumab.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.5 Duration of Follow-Up

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

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 CDX-1127 (varlilumab) and Atezolizumab (all participants)

7.1.1 General AE Management and Dose Modification Guidelines

Dosing of both CDX-1127 (varlilumab) and atezolizumab is fixed with no dose-modification permitted. Both CDX-1127 (varlilumab) and atezolizumab should always be administered on the same day. Monotherapy with atezolizumab or CDX-1127 (varlilumab) alone is not permitted.

On cycle 1 day 1 (first dose), patients will be observed for at least 4 hours after the last study drug administration to monitor for infusion reaction/cytokine release syndrome/hypersensitivity reaction. For all subsequent doses/cycles, patients should be monitored for at least 1 hour following the last administration of study drug. Infusions should be given in a monitored setting that has ready access to an intensive care unit in case of a severe infusion reaction. Acetaminophen may be used to manage drug-related adverse events such as fever, myalgias or arthralgias and anti-histamines may be used to manage drug-related adverse events such pruritus.

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 and CDX-1127 (varlilumab) are held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab-CDX-1127 (varlilumab) 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-CDX-1127 (varlilumab) may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

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

Because of this, the algorithm used for the management of adverse events associated with atezolizumab monotherapy will be applied to the management of adverse events associated with atezolizumab-CDX-1127 (varlilumab) combination therapy. Guidelines for management of atezolizumab-associated adverse events described in depth below (Section 7.1.2 have been amended from “atezolizumab” alone to apply both “atezolizumab and CDX-1127 (varlilumab)” as a single treatment unit.

Generally speaking, patients receiving CDX-1127 (varlilumab) and atezolizumab should be monitored for signs and symptoms of enterocolitis, dermatitis, hepatotoxicity, neuropathy, pulmonary toxicity and endocrinopathy. Patients should be advised to immediately report symptoms such as unexplained abdominal pain, diarrhea, nausea or vomiting, severe rash or vision changes. Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. Laboratory tests must be performed as outlined in study calendar. Visual complaints should be investigated by an ophthalmologist.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab and CDX-1127 (varlilumab); for higher-grade irAEs, atezolizumab and CDX-1127 (varlilumab) should both be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding of both atezolizumab & CDX-1127 (varlilumab) and/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 and CDX-1127 (varlilumab). Atezolizumab and CDX-1127 (varlilumab) should both be permanently discontinued in patients with life-threatening irAEs.

Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the respective mechanisms of action of atezolizumab and CDX-1127 (varlilumab), systemic immune activation is considered a potential risk when given in combination. 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 CDX-1127 (varlilumab), 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.

7.1.2 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 and CDX-1127 (varlilumab) Investigator's Brochure. See **Section 6.1.1** for guidelines for the management of Infusion Related Reactions and Anaphylaxis or otherwise follow institutional protocol.

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

Immune-mediated Cardiac Events

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

Immune-mediated Myocarditis

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

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

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

Immune-mediated Pericardial Disorders

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

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient

presenting with chest pain associated with dyspnea or hemodynamic instability.

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

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

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

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

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 measured 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. . Management guidelines for neurologic disorders, and specific guidelines for myelitis, are provided in the tables below.

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

Event	Management

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

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

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

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

Event	Management
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

For recommendations to hold atezolizumab and CDX-1127 (varlilumab) and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab and CDX-1127 (varlilumab) therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab and CDX-1127 (varlilumab) can be resumed.
- Atezolizumab and CDX-1127 (varlilumab) 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.

7.2 Cobimetinib plus Atezolizumab and CDX-1127 (varlilumab) (Treatment Arm A patients only)

7.2.1 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 &CDX-1127 (varlilumab) are included in Section 7.3. 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[b] 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.
[b] An exception to this is for Grade 3 anemia, without presence of hemorrhage and/or hemolytic process. In this case, participants can be treated with transfusions as needed in order to improve to grade 2 or better and do not require treatment interruption or dose

reduction. If recurrent transfusions are needed, treating provider can consider dose reduction.

Toxicities will be evaluated using NCI CTCAE v5.0. If toxicity occurs, the toxicity will be graded and appropriate supportive care treatment will be administered to decrease symptoms.

Generally, in the case of Grade 4 hematologic or Grade 3 to 4 non-hematologic toxicity (except for Grade 3 skin cancer, squamous or basal cell type), treatment with cobimetinib should be interrupted until recovery to baseline or Grade 1 and then resumed at one dose level reduction. 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

Up to two dose reductions of cobimetinib will be allowed as follows: 40 mg PO daily and then 20 mg PO daily for 21 days of a 28-day cycle. In the case of recurrent toxicity after two dose reductions, cobimetinib should be discontinued

7.2.2 Management of Cobimetinib plus Atezolizumab and CDX-1127 (varlilumab)−Associated Adverse Events of particular concern (Treatment Arm A)

Due to the triplet combination acting through a range of mechanisms with potential overlapping and also distinct adverse events (AE), patients who experience intolerance or adverse events should be carefully evaluated to examine whether the AE can attributable to one of the two classes of therapies: 1) targeted therapy (cobmitinib); 2) immunotherapy [Atezolizumab and CDX-1127 (varlilumab)]. For example, a patient removed from cobimetinib therapy after developing retinal vein occlusion may continue on with their Atezolizumab and CDX-1127 (varlilumab) combination. If there is ambiguity regarding the responsible drug/class of drug, all three agents should be held/discontinued with special consideration for full/partial regimen resumption as indicated by management guidelines detailed in section 7.3.

Below are recommended management of specific adverse events of particular concern with the triplet combination therapy are provided here.

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.

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.

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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.

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.

OCULAR 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.

DECREASED LEFT VENTRICULAR EJECTION FRACTION (LVEF)
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.

Decreased LVEF may also result from immune related cardiomyopathy, a potential risk of atezolizumab therapy. For this reason, atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) may be restarted only if the patient is clinically stable, and after consultation with the trial PI.

ELEVATED CPK
Elevated CPK has been reported with cobimetinib. Recommended Dose Modifications for Cobimetinib in Patients with CPK Elevations are presented below in section 7.3.

HEMORRHAGE
Bleeding complications have been associated with cobimetinib treatment. There is no data on the effectiveness of cobimetinib dose modification for hemmorhagic events.

7.3 AE Management and Dose Interruption/Modification Guidelines

AE Management and Dose Interruption Guidelines for Specific Toxicities			
Toxicity	Severity/ Duration	Management	
		CDX-1127 (varlilumab) & Atezolizumab	Cobimetinib plus CDX-1127 (varlilumab) & Atezolizumab
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	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).	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).
Adrenal insufficiency * Hypohysitis (pan-hypopituarism)	Grade 2+ (symptomatic)	Hold Atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) according to the guidelines above.	Hold Atezolizumab & CDX-1127 (varlilumab) and cobimetinib 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 & CDX-1127 (varlilumab)

		For recurrent hypophysitis, treat as a Grade 4 event. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if event does not resolve to grade 1 or better or patient is not stable on replacement therapy within 12 weeks.	and cobimetinib at same doses For recurrent hypophysitis, treat as a Grade 4 event. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib 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 & CDX-1127 (varlilumab). Monitor amylase and lipase prior to dosing.	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Monitor amylase and lipase prior to dosing.
	Grade 2	Continue atezolizumab & CDX-1127 (varlilumab). Monitor amylase and lipase weekly. For prolonged elevation (*e.g.*, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. **Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN:** Treat as a Grade 3 event.	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Monitor amylase and lipase weekly. For prolonged elevation (*e.g.*, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. **Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN:** Treat as a Grade 3 event.
	Grade 3 or 4	Hold atezolizumab & CDX-1127 (varlilumab).	Hold atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) according to the guidelines above. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab & CDX-1127 (varlilumab).	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 & CDX-1127 (varlilumab) at previous fixed and cobimetinib with 1 dose-level reduction. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib.
Anemia	Grade 3 Without presence of active hemorrhage or immune-mediated hemolysis	Continue atezolizumab & CDX-1127 (varlilumab). Transfuse prn to Grade ≤2 or resolution of symptomatic anemia Monitor CBC weekly	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib Transfuse prn to Grade ≤2 or resolution of symptomatic anemia

		Workup for etiologies of anemia	Monitor CBC weekly Workup for etiologies of anemia For recurrent grade 3 anemia, can consider 1 dose level reduction for cobimetinib
Cardiac Event – Decreased Left Ventricular Ejection Fraction (LVEF)	Asymptomatic, absolute decrease in LVEF from baseline of greater than 10% and LVEF less than 50%	Hold atezolizumab & varlilumab. Assess for symptoms and complete work up. Repeat ECHO in 2 weeks. Work up should generally include troponin, CPK, EKG, echocardiogram and/or cardiac MRI, and cardiology consultation Resume atezolizumab & CDX-1127 (varlilumab) at fixed dose if all of the following are present • LVEF is 50% or greater, OR • Absolute decrease from baseline LVEF is more than 10% Permanently discontinue atezolizumab & CDX-1127 (varlilumab)* if any of the following are present • LVEF is 50% or greater, AND • Absolute decrease from baseline LVEF is more than 10% * If etiology of	Hold atezolizumab, CDX-1127 (varlilumab), and cobimetinib. Assess for symptoms and complete work up. Repeat ECHO in 2 weeks. Work up should generally include troponin, CPK, EKG, echocardiogram and/or cardiac MRI, and cardiology consultation Resume atezolizumab & CDX-1127 (varlilumab) at fixed dose and cobimetinib at next lower dose if all of the following are present • LVEF is 50% or greater, OR • Absolute decrease from baseline LVEF is more than 10% Permanently discontinue atezolizumab & CDX-1127 (varlilumab)* and cobimetinib any of the following are present • LVEF is 50% or greater, AND • Absolute decrease from

		decreased LVEF can be confidently attributed to a non-immune-mediated etiology, LVEF is > 40% (or ≤ 10% absolute decrease from BL) and myocarditis has been excluded, resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose can be considered on case by case basis with discussion & approval by trial PI. For patients with more severe reductions in the LVEF, atezolizumab & CDX-1127 (varlilumab) may be restarted only if the patient is clinically stable, and after consultation with the trial PI.	baseline LVEF is more than 10% *If etiology of decreased LVEF can be confidently attributed to cobimetinib alone or a non-immune-mediated etiology , LVEF is > 40% (or ≤ 10% absolute decrease from BL) and myocarditis has been excluded, resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose can be considered on case by case basis with discussion & approval by trial PI. For patients with more severe reductions in the LVEF, atezolizumab & CDX-1127 (varlilumab) may be restarted only if the patient is clinically stable, and after consultation with the trial PI.
	Symptomatic LVEF decrease from baseline	Withhold atezolizumab & CDX-1127 (varlilumab) for up to 4 weeks; repeat LVEF Work up should generally include troponin, CPK, EKG, echocardiogram and/or cardiac MRI, and cardiology consultation Resume atezolizumab & CDX-1127 (varlilumab) at fixed dose if all of the following are present • Symptoms	Withhold atezolizumab & CDX-1127 (varlilumab) and cobimetinib for up to 4 weeks; repeat LVEF Work up should generally include troponin, CPK, EKG, echocardiogram and/or cardiac MRI, and cardiology consultation Resume atezolizumab & CDX-1127 (varlilumab) at fixed dose and cobimetinib at next

		resolved, and • LVEF is 50% or greater, OR • Absolute decrease from baseline LVEF is 10% or less Permanently discontinue atezolizumab & CDX-1127 (varlilumab)* if any of the following are present • Symptoms persist, or • Symptoms resolved, but LVEF is less than 50% andAbsolute decrease from baseline LVEF is more than 10% * If etiology of decreased LVEF can be confidently attributed to a non-immune-mediated etiology, LVEF is > 40% (or ≤ 10% absolute decrease from BL) and myocarditis has been excluded, resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose can be considered on case by case basis with discussion & approval by trial PI. For patients with more severe reductions in the LVEF, atezolizumab & CDX-1127 (varlilumab) may be restarted only if the patient is clinically stable, and after	lower dose if all of the following are present • Symptoms resolved, and • LVEF is 50% or greater, OR • Absolute decrease from baseline LVEF is 10% or less Permanently discontinue atezolizumab & CDX-1127 (varlilumab)* and cobimetinib any of the following are present • Symptoms persist, or • Symptoms resolved, but LVEF is less than50% and Absolute decrease from baseline LVEF is more than 10% *If etiology of decreased LVEF can be confidently attributed to cobimetinib alone or a non-immune-mediated etiology , LVEF is > 40% (or ≤ 10% absolute decrease from BL) and myocarditis has been excluded, resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose can be considered on case by case basis with discussion & approval by trial PI. For patients with more severe reductions in the LVEF,

		consultation with and approval from the trial PI.	atezolizumab & CDX-1127 (varlilumab) may be restarted only if the patient is clinically stable, and after consultation with and approval from the trial PI.
Creatine Kinase (CPK) Elevation	General Guidance	Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). Permanently discontinue atezolizumab & CDX-1127 (varlilumab) 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.	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). Permanently discontinue atezolizumab & CDX-1127 (varlilumab) 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.
	Grade 3 that are asymptomatic and deemed not clinically significant	Hold atezolizumab & CDX-1127 (varlilumab) 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 & CDX-	Hold atezolizumab & CDX-1127 (varlilumab) 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.

		1127 (varlilumab) at fixed dosage only if cardiac etiology is ruled out. Recheck CPK at least once a week. If CPK remains Grade 3 or decreases, continue Atezolizumab & CDX-1127 (varlilumab) at fixed dosage.	Atezolizumab & CDX-1127 (varlilumab) 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 Atezolizumab & CDX-1127 (varlilumab) and cobimetinib at fixed dosage and cobimetinib at current dose and schedule.
	Grade 4 CPK elevations or any grade CPK with clinically significant effect (signs of cardiac injury and/or renal injury)	Hold atezolizumab & CDX-1127 (varlilumab). Work up and treat per institutional guidelines. Rule out immune-related cardiomyopathy, myocarditis, other cardiac conditions, and myoglobin-induced kidney injury. Recheck CPK within 3 days. When CPK is Grade ≤ 3 and cardiac immune-related cardiomyopathy has been ruled out, atezolizumab & CDX-1127 (varlilumab) may be resumed Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if Grade 4 CPK elevation recurs or if there is evidence of cardiac/renal	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Work up and treat per institutional guidelines. Rule out immune-related cardiomyopathy, myocarditis, other cardiac conditions, and myoglobin-induced kidney injury. Recheck CPK within 3 days. When CPK is Grade ≤ 3 and cardiac immune-related cardiomyopathy has been ruled out, atezolizumab & CDX-1127 (varlilumab) 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

		injury with any instance of CPK elevation*. *If non-immune related etiology is most likely, resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose will require consultation with and approval by study PI	elevation recurs after 1 dose reduction, cobimetinib may be reduced by another dose level (e.g., 40 to 20 mg). Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib if Grade 4 CPK elevation recurs after 2 dose reductions of cobimetinib OR if there is evidence of cardiac/renal injury associated with any instance CPK elevation. *If non-immune related etiology is most likely, resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose without cobimetinib will require consultation with and approval by study PI
Dermatologic toxicity/rash (*e.g.*, maculopapular or purpura)	Grade 1	Continue atezolizumab & CDX-1127 (varlilumab). Initiate symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).	Continue atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab). Consider consultation with a dermatologist for evaluation and if indicated, biopsy. 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	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Consider consultation with a dermatologist. Administer topical steroids. Consider higher potency topical steroids if rash does not improve. For acneiform rash, administer topical corticosteroids (hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) for at least the 6 weeks. For an initial grade 2 rash that is considered attributable to Cobimetinib and remains grade 2 at the start of the next cycle, despite appropriate topical treatments and oral antibiotics, continue atezolizumab & CDX-1127 (varlilumab) at fixed dose, but can consider holding cobimetinib until resolution to grade 1 or

			lower. Cobimetinib should be reduced one dose level.
	Grade 3	Hold atezolizumab & CDX-1127 (varlilumab). Refer patient to dermatologist for evaluation and if indicated, biopsy. Administer oral prednisone 10 mg or equivalent. If the event does not improve within 48–72 hours, increase dose to1–2 mg/kg/day or equivalent. Restart atezolizumab & CDX-1127 (varlilumab) if event resolves to grade 2 (tolerable) or better within 12 weeks. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if event does not resolve to tolerable grade 2 or better within 12 weeks.	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Refer patient to 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. For acneiform rash, consider continuation of topical corticosteroids 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline or antibiotics covering skin flora) for at least 6 weeks Restart atezolizumab & CDX-1127 (varlilumab) at fixed dose and cobimetinib at 1 dose reduction if rash resolves to ≤ tolerable grade 2, and systemic dose is less than or equal to 10 mg oral prednisone equivalent per day.
	Grade 4	Permanently discontinue atezolizumab & CDX-1127 (varlilumab).	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and

		Patient may not resume treatment, regardless of benefit. Otherwise, manage as above.	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.	A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated.
	Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Withhold atezolizumab & CDX-1127 (varlilumab) for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. Follow the applicable treatment and management guidelines above. If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab& CDX-1127 (varlilumab)	Withhold atezolizumab & CDX-1127 (varlilumab) and cobimetinib for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. Follow the applicable treatment and management guidelines above. If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib.
Diarrhea or colitis	Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.	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.	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 & CDX-1127 (varlilumab). 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	Continue atezolizumab, CDX-1127 (varlilumab) 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.	Endoscopy is recommended if symptoms persist for >7 days. Monitor closely.
	Grade 2	Hold atezolizumab & CDX-1127 (varlilumab). 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 for endoscopy is recommended. For initial event that persist for ≤5 days, and do not require steroids, restart atezolizumab & CDX-1127 (varlilumab) at fixed dose once event	Hold atezolizumab, CDX-1127 (varlilumab), 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 for endoscopy is recommended. For initial event that persist for ≤5 days, and do not require steroids, restart atezolizumab & CDX-1127 (varlilumab)

		grade ≤ 1 <u>For recurrent and/or events lasting >5 days:</u> For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If recurrent event and/or event persist >5 days, requires steroids, and resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab & CDX-1127 (varlilumab) once event grade ≤ 1. For recurrent events or events that persist >5 days, require steroids, but event DOES NOT resolves to grade 1 or better within 12 weeks, permanently discontinue atezolizumab & CDX-1127 (varlilumab)* *Resumption of atezolizumab & CDX-1127 (varlilumab) may be considered, after consultation with the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event.	at fixed dosea and cobimetinib at 1 dose reduction once grade ≤ 1 <u>For recurrent and/or events lasting >5 days:</u> For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. For recurrent events or events that persist >5 days, requiring steroids, and event resolves to grade 1 or better within 12 weeks, restart atezolizumab & CDX-1127 (varlilumab) at fixed dose and cobimetinib at 1 dose reduction once event grade ≤ 1. For recurrent events or events that persist >5 days, require steroids, but event DOES NOT resolves to grade 1 or better within 12 weeks, permanently discontinue combimetinib plus atezolizumab & CDX-1127 (varlilumab)* *Resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose and cobimetinib at 1 level dose reduction after consultation with the

			trial PI, in patients who are deriving benefit treatment benefit and have fully recovered.
	Grade 3	Hold atezolizumab & CDX-1127 (varlilumab). 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 does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. For events that require steroids, but event DOES NOT resolves to grade 1 or better within 12 weeks, permanently discontinue atezolizumab & CDX-1127 (varlilumab)* For events that require	Hold atezolizumab & CDX-1127 (varlilumab) 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 does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and restart atezolizumab & CDX-1127 (varlilumab) at fixed doses and cobimetinib at 1 dose reduction once at baseline stool frequency. For events that require steroids, but event DOES NOT resolves to grade 1 or better within 12 weeks, permanently discontinue

		steroids AND biologic immunosuppressive therapy (e.g. infliximab, mycophenolate mofetil, etc.,.) but event DOES resolves to grade 1 or better within 12 weeks, permanently discontinue atezolizumab & CDX-1127 (varlilumab)* *Resumption of atezolizumab & CDX-1127 (varlilumab) may be considered after consultation with and approval from the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event For events that require steroids AND biologic immunosuppressive therapy (e.g. infliximab, mycophenolate mofetil, etc.,.) but event DOES NOT resolves to grade 1 or better within 12 weeks, permanently discontinue atezolizumab & CDX-1127 (varlilumab). <u>Patient may not resume treatment, regardless of benefit</u>	combimetinib plus atezolizumab & CDX-1127 (varlilumab)* For events that require steroids AND biologic immunosuppressive therapy (e.g. infliximab, mycophenolate mofetil, etc.,.) but event DOES resolves to grade 1 or better within 12 weeks, permanently discontinue combimetinib plus atezolizumab & CDX-1127 (varlilumab)* *Resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose and cobimetinib at 1 level dose reduction can be considered after consultation with and approval from trial PI, in patients who are deriving benefit treatment benefit and have fully recovered. For events that require steroids AND biologic immunosuppressive therapy (e.g. infliximab, mycophenolate mofetil, etc.,.) but event DOES NOT resolves to grade 1 or better within 12 weeks, permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. <u>Patient may not resume treatment, regardless of benefit.</u>

	Grade 4	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). 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.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) 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. 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.

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome	Suspected HLH or MAS	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). Consider patient referral to hematologist. Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. If event does not respond to treatment within 24 hours, initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée *et al*., 2019). If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Consider patient referral to hematologist. Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. If event does not respond to treatment within 24 hours, initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée *et al*., 2019). If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Hemorrhage	Grade 3 events:	Continue atezolizumab & CDX-1127 (varlilumab)	Continue atezolizumab & CDX-1127 (varlilumab) Hold cobimetinib If improved to Grade 0 or 1, resume at the next lower dose level. If not improved within 4 weeks, permanently discontinue

	Grade 4 events or Cerebral hemorrhage (all grades):	Consultation with study PI prior to continue atezolizumab & CDX-1127 (varlilumab)	Continue atezolizumab & CDX-1127 (varlilumab) Permanently discontinue cobimetinib.
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 & CDX-1127 (varlilumab). The differential diagnosis of acute abdominal pain should also include pancreatitis, as described below.	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 & CDX-1127 (varlilumab). The differential diagnosis of acute abdominal pain should also include pancreatitis, as described below.
	Hepatic event, general guidance	Consider possible tumor-related etiology, and consider earlier restaging imaging to inform clinical decision making (e.g. steroid initiation)	Consider possible tumor-related etiology, and consider earlier restaging imaging to inform clinical management (e.g. steroid initiation)
	Grade 1 hepatic event	Continue atezolizumab & CDX-1127	Continue atezolizumab & CDX-1127

		(varlilumab). Monitor LFTs weekly until values resolve to within baseline values.	(varlilumab) and cobimetinib. Monitor LFTs weekly until values resolve to within normal limits.
	Grade 2 hepatic event, ≤5 days **includes:* AST/ALT is >ULN to ≤3×ULN at baseline and increases to >5×ULN to ≤10×ULN	Continue atezolizumab & CDX-1127 (varlilumab). Monitor LFTs biweekly until values resolve to baseline values.	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Monitor LFTs biweekly until values resolve to baseline values.
	Grade 2 hepatic event, >5 days **includes:* AST/ALT is >ULN to ≤3×ULN at baseline and increases to >5×ULN to ≤10×ULN	Hold atezolizumab & CDX-1127 (varlilumab). Work to evaluate etiology of hepatic event. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury If suspicion for immune-mediated process is high, 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 & CDX-1127 (varlilumab) if event does not resolve to	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Work up to evaluate etiology of hepatic event. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury If suspicion for immune-mediated process is high, 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 & CDX-1127 (varlilumab) at fixed doses and cobimetinib at 1 dose reduction.

		Grade 1 or better within 12 weeks. Resumption of atezolizumab atezolizumab & CDX-1127 (varlilumab) and cobimetinib at 1 level dose reduction may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab & CDX-1127 (varlilumab) and cobimetinib should be based on investigator's assessment of benefit–risk, discussion with PI, and documented by the investigator (or an appropriate delegate)	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab atezolizumab & CDX-1127 (varlilumab) and cobimetinib at 1 level dose reduction may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab & CDX-1127 (varlilumab) and cobimetinib should be based on investigator's assessment of benefit–risk, discussion with PI, and documented by the investigator (or an appropriate delegate)
	Grade 3 or 4 hepatic event	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If suspicion for immune-mediated process is high, initiate treatment with 1–2 mg/kg/day oral	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and hold cobimetinib. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. If suspicion for immune-mediated process is high, initiate treatment

		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 atezolizumab atezolizumab & CDX-1127 (varlilumab) may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). For grade 3 AEs, patient may only resume after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.	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 atezolizumab atezolizumab & CDX-1127 (varlilumab) and cobimetinib at 1 level dose reduction may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab & CDX-1127 (varlilumab) and cobimetinib should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). For grade 3 AEs, patient may only resume after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.

Hyperglycemia	Grade 1 or 2	Continue atezolizumab & CDX-1127 (varlilumab) Initiate treatment with insulin if needed. Monitor for glucose control. Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence may be an indication of beta-cell destruction and atezolizumab-induced diabetes. If patient has Type 1 diabetes (*e.g.* new-onset diabetes in the absence of corticosteroids or another inciting medication), treat as a Grade 3 event. Exercise caution in utilizing non-insulin hypoglycemic agents in this setting, as new-onset hyperglycemia in the absence of corticosteroids may be an indication of beta-cell destruction and atezolizumab-induced diabetes. After a thorough investigation of other potential causes which may involve a referral to an endocrinologist, follow institutional guidelines.	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib Initiate treatment with insulin if needed. Monitor for glucose control. Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence may be an indication of beta-cell destruction and atezolizumab-induced diabetes. If patient has Type 1 diabetes (*e.g.* new-onset diabetes in the absence of corticosteroids or another inciting medication), treat as a Grade 3 event. Exercise caution in utilizing non-insulin hypoglycemic agents in this setting, as new-onset hyperglycemia in the absence of corticosteroids may be an indication of beta-cell destruction and atezolizumab-induced diabetes. After a thorough investigation of other potential causes which may involve a referral to an endocrinologist, follow institutional guidelines.

	Grade 3 or 4	Hold atezolizumab & CDX-1127 (varlilumab). Initiate treatment with insulin. Monitor for glucose control. Strongly consider referral to endocrinologist, consider obtaining C-peptide level paired with glucose, autoantibody levels (*e.g*. GAD65, islet cell autoantibodies), and hemoglobin A1C level. If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g*. anion gap, ketones, blood pH, etc.) reported. Resume atezolizumab & CDX-1127 (varlilumab) when symptoms resolve and glucose levels are stable.	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib Initiate treatment with insulin. Monitor for glucose control. Strongly consider referral to endocrinologist, consider obtaining C-peptide level paired with glucose, autoantibody levels (*e.g*. GAD65, islet cell autoantibodies), and hemoglobin A1C level. If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g*. anion gap, ketones, blood pH, etc.) reported. Resume atezolizumab & CDX-1127 (varlilumab) and cobimetinib when symptoms resolve and glucose levels are stable.
Hyperthyroidism	Grade 1 (asymptomatic)	TSH ≥ 0.1 mU/L and < 0.5 mU/L: Continue atezolizumab & CDX-1127 (varlilumab) Monitor TSH every 4 weeks.	TSH ≥ 0.1 mU/L and < 0.5 mU/L: Continue atezolizumab & CDX-1127 (varlilumab) Monitor TSH every 4 weeks.

		TSH < 0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism.	TSH < 0.1 mU/L: Follow guidelines for symptomatic hyperthyroidism
	Grade 2+ (symptomatic)	Hold atezolizumab & CDX-1127 (varlilumab) Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab & CDX-1127 (varlilumab) when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) for life-threatening immune-related hyperthyroidism.	Hold atezolizumab & CDX-1127 (varlilumab) and combimetinib Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab & CDX-1127 (varlilumab) and cobimetinib when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobmetinib* for life-threatening immune-related hyperthyroidism.
Hypothyroidism	Grade 1-2	Continue atezolizumab & CDX-1127 (varlilumab) Start thyroid-replacement hormone. Monitor TSH weekly.	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib Start thyroid-replacement hormone. Monitor TSH weekly.
	Grades 3-4	Hold atezolizumab & CDX-1127 (varlilumab) Start thyroid-replacement hormone. Consider referral to an	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib Start thyroid-replacement hormone.

		endocrinologist. Monitor TSH weekly. Restart atezolizumab & CDX-1127 (varlilumab) when symptoms are controlled and thyroid function is improving.	Consider referral to an endocrinologist. Monitor TSH weekly. Restart atezolizumab & CDX-1127 (varlilumab) and cobimetinib when symptoms are controlled and thyroid function is improving.
Infusion Reactions	Grade 1 [a] Fever [b] with or without constitutional symptoms	Immediately interrupt infusion. Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. If symptoms recur, discontinue infusion of this dose. Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. For subsequent infusions, consider	Immediately interrupt infusion. Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. If symptoms recur, discontinue infusion of this dose. Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. For subsequent infusions, consider

		administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.	administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
	Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	Immediately interrupt infusion. Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. If symptoms recur, discontinue infusion of this dose. Administer symptomatic treatment. [c] For hypotension, administer IV fluid bolus as needed. Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and	Immediately interrupt infusion. Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. If symptoms recur, discontinue infusion of this dose. Administer symptomatic treatment. [c] For hypotension, administer IV fluid bolus as needed. Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup

		symptoms of HLH or MAS as described in this appendix. Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. [e] If symptoms resolve to Grade 1 or better for 3 consecutive days, the next infusion may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the investigator.	and assess for signs and symptoms of HLH or MAS as described in this appendix. Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. [e] If symptoms resolve to Grade 1 or better for 3 consecutive days, the next infusion may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the

			investigator.
	Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	Permanently discontinue atezolizumab. e Administer symptomatic treatment. c For hypotension, administer IV fluid bolus and vasopressor as needed. Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. e Administer symptomatic treatment. c For hypotension, administer IV fluid bolus and vasopressor as needed. Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy.

		initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator. Atezolizumab & CDX-1127 (varlilumab) may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, <u>but only after consultation with the trial Principal Investigator</u>	Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator. Atezolizumab & CDX-1127 (varlilumab) and cobimetinib may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, <u>but only after consultation with the trial Principal Investigator</u>
	<u>Grade 4</u> [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **<u>and/or</u>** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP,	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). [e] Administer symptomatic treatment. [c] Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. [e] Administer symptomatic treatment. [c] Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor

	intubation and mechanical ventilation)	closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator. Hospitalize patient until complete resolution of symptoms.	other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator. Hospitalize patient until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.
Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading. [b] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia. [c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice. [d] Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min. [e] Resumption of study therapy may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with study therapy should be based on investigator's assessment of benefit–risk, discussion and approval of PI, and documented by the investigator (or an appropriate delegate). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio. [f] Refer to Riegler *et al*. (2019).			
Meningo-encepahlitis, immune-related (signs and symptoms in absence of an identified alternate etiology)	All grades	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). <u>Patient may not resume treatment, regardless of benefit.</u> 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 resolves to grade 1 or better, taper corticosteroids over ≥1 month. If event does not	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. <u>Patient may not resume treatment with atezolizumab & CDX-1127 (varlilumab) and cobimetinib, regardless of benefit.</u> 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 resolves to grade 1 or better, taper corticosteroids over ≥1

		improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.	month. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Myasthenia gravis and Guillain-Barré syndrome	All grades	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). Patient may not resume treatment, regardless of benefit. See Section 7.1.2 for further instructions.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Patient may not resume treatment with atezolizumab & CDX-1127 (varlilumab) and cobimetinib, regardless of benefit. See Section 7.1.2 for further instructions.
Myocarditis (immune-related)	Grades 2-4	Permanently discontinue atezolizumab and CDX-1127 (varlilumab) and contact the study PI. See Section 7.1.2 for further instructions.	Permanently discontinue atezolizumab and CDX-1127 (varlilumab) and cobimetinib contact the study PI. See Section 7.1.2 for further instructions.
Myositis	Grade 1	Continue atezolizumab & CDX-1127 Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines.	Continue atezolizumab & CDX-1127 and cobimetinib Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines.
	Grade 2	Withhold atezolizumab & CDX-1127 (varlilumab). Refer patient to rheumatologist or	Withhold atezolizumab & CDX-1127 (varlilumab) and cobimetinib. [a] Refer patient to

		neurologist. Initiate treatment as per institutional guidelines. Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume. If event does not resolve to Grade 1 or better while withholding infusions, permanently discontinue infusions. [c]	rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume infusions at some dose and cobimetinib at 1 dose reduction. If event does not resolve to Grade 1 or better while withholding study therapy, permanently discontinue therapy. [c]
	Grade 3	Withhold atezolizumab & CDX-1127 (varlilumab). Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines.	Withhold atezolizumab & CDX-1127 (varlilumab). Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines.

		Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume study therapy. If event does not resolve to Grade 1 or better while withholding study therapy, permanently discontinue. For recurrent events, treat as a Grade 4 event.	Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume infusions at some dose and cobimetinib at 1 dose reduction. If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment. For recurrent events, treat as a Grade 4 event.

	Grade 4	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). [c] Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. [c] Refer patient to rheumatologist or neurologist. Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Neuropathy, immune-related (sensory and/or motor)	All Grades Grade 1	See Section 7.1.2 for further instructions.	See Section 7.1.2 for further instructions.
Ocular events – inflammation (e.g. uveitis, iritis or episcleritis)	Grade 1	Continue atezolizumab & CDX-1127 (varlilumab) Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.	Continue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
	Grade 2 (Symptomatic)	Hold atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) according to the guidelines above. Permanently discontinue atezolizumab & CDX-	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib. 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 & CDX-1127 (varlilumab) according to the guidelines above.

		1127 (varlilumab) if event does not resolve to grade 1 or better within 12 weeks.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and combimetinib for immune−mediated ocular disease that is unresponsive to immunosuppressive therapy.
	Grade 3 or 4	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). 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 consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and combimetinib. 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 consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.
Ocular Events - 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 & CDX-1127 (varlilumab) Continue ophthalmology follow-up as clinically indicated.	Continue atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) and cobimetinib dosing should be held until symptoms improve to Grade 1. Restart atezolizumab & CDX-1127 (varlilumab) at fixed doses. If no recovery within 4 weeks or if Grade 2 or 3 serous retinopathy recurs, discuss permanent discontinuation of atezolizumab & CDX-1127 (varlilumab) with study PI.	Hold atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) and cobimetinib dosing should be held until symptoms improve to Grade 1. Restart atezolizumab & CDX-1127 (varlilumab) at fixed doses 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, atezolizumab & CDX-1127 (varlilumab)* and

			cobimetinib should be permanently discontinued. *Resumption of atezolizumab & CDX-1127 (varlilumab) at fixed dose without cobimetinib can be considered only after consultation with and approval by the trial PI, in patients who are deriving benefit treatment benefit and have fully recovered.
	Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue atezolizumab & CDX-1127 (varlilumab).	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib.
Ocular Events – Rentinal Vein Occlusion (RVO)	RVO Any grade	RVO work up and treatment per institutional guidelines. Atezolizumab & CDX-1127 (varlilumab) therapy may be continued.	If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. Atezolizumab & CDX-1127 (varlilumab) therapy may be continued.

Pancreatitis, immune related	Grade 2 or 3	Hold atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) according to the guidelines above. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab). <u>Patient may not resume treatment, regardless of benefit.</u>	Hold atezolizumab & CDX-1127 (varlilumab) and cobimetinib 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 & CDX-1127 (varlilumab) and cobimetinib at same doses. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib 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 & CDX-1127 (varlilumab) and cobimetinib. <u>Patient may not resume treatment, regardless of benefit.</u>

	Grade 4	Permanently discontinue atezolizumab & CDX-1127 (varlilumab). 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. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. 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. 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.	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 & CDX-1127 (varlilumab) and monitor	Continue atezolizumab & CDX-1127 (varlilumab) and

		closely. Re-evaluate on serial imaging. Consider patient referral to a pulmonary specialist. For recurrent pneumonitis, treat as a grade 3 or 4 event.	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 & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) according to the guidelines above. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab & CDX-1127 (varlilumab) can be	Hold atezolizumab & CDX-1127 (varlilumab) 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 & CDX-1127 (varlilumab) at fixed doses and cobimetinib at 1 dose reduction if GGO/infiltrates improving. If corticosteroids have been initiated, they must be tapered over ≥ 1

		resumed. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.	month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab & CDX-1127 (varlilumab) and cobimetinib can be resumed. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
	Grade 3 or 4	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) Bronchoscopy or BAL is recommended. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent	Permanently discontinue atezolizumab & CDX-1127 (varlilumab) and cobimetinib. Bronchoscopy or BAL is recommended. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If corticosteroids have been initiated, they must be tapered over ≥ 1

		of ≤10 mg/day oral prednisone before atezolizumab & CDX-1127 (varlilumab) can be resumed. For grade 3 AEs, patient may only resume treatment with fixed dose atezolizumab & CDX-1127 (varlilumab) after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.	month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab & CDX-1127 (varlilumab) and cobimetinib can be resumed. For grade 3 AEs, patient may only resume treatment with fixed dose atezolizumab & CDX-1127 (varlilumab) and 1 – level dose reduced cobimetinib after consultation with the trial PI. For grade 4, patient cannot resume treatment, regardless of benefit.
Renal Dysfunction	Renal event, general guidance	Consider possible tumor-related etiology, and consider earlier restaging imaging to inform clinical decision making (e.g. steroid initiation)	Consider possible tumor-related etiology, and consider earlier restaging imaging to inform clinical management (e.g. steroid initiation)
	Grade 2 increased serum creatinine/CrCl	Withhold atezolizumab & CDX-1127 (varlilumab) Refer to renal specialist for evaluation, work up and consideration of kidney biopsy to establish etiology of kidney event If immune-related etiology highly suspected following work up, initiate treatment with corticosteroids equivalent to	Withhold atezolizumab & CDX-1127 (varlilumab) & cobimetinib Refer to renal specialist for evaluation, work up and consideration of kidney biopsy to establish etiology of kidney event If immune-related etiology highly suspected following work up, initiate treatment with corticosteroids

		1–2 mg/kg/day oral prednisone. Resume in patients with complete or partial resolution (Grade 0 to 1) after appropriate intervention Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids	equivalent to 1–2 mg/kg/day oral prednisone. Resume in patients with complete or partial resolution (Grade 0 to 1) after appropriate intervention. Consider cobimetinib dose reduction if contributing to event Permanently discontinue atezolizumab & CDX-1127 (varlilumab) & cobimetinib if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids
	Grade 3 or 4 increased serum creatinine/CrCl	Discontinue atezolizumab & CDX-1127 (varlilumab) Work to evaluate etiology of renal event. Refer to renal specialist for evaluation, work up and consideration kidney biopsy to establish etiology of kidney event If immune-related etiology highly suspected following work up, initiate treatment with corticosteroids equivalent to	Discontinue atezolizumab & CDX-1127 (varlilumab) & cobimetinib Refer to renal specialist for evaluation, work up and consideration kidney biopsy to establish etiology of kidney event If immune-related etiology highly suspected following work up, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.

		1–2 mg/kg/day oral prednisone. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper at same doses. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids 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.	Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper at same doses. Permanently discontinue atezolizumab & CDX-1127 (varlilumab) & cobimetinib if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment (infusions at same dose, and cobimetinib at one dose reduction) after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agents

8.1.1 Atezolizumab (NSC 783608)

Other Names: Tecentriq™, MPDL3280A

Classification: monoclonal antibody

M.W.: 150 KD

Mode of Action: anti-PD-L1

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

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

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

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-

46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

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

Route of Administration: IV infusion

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

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

Patient Care Implications:
Male patients and female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 150 days after the last dose of atezolizumab or 3 months after the last dose of cobimetinib.

Availability

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

8.1.2 [redacted]

[redacted]

Availability

CDX-1127 (varlilumab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.3 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. For this reason, women of child-

bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and, for the duration of study participation, and 5 months after the last dose of Atezolizumab and 3 months after the last dose of cobimetinib.

Availability

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

8.1.4 Agent Ordering and Agent Accountability

8.1.4.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

Sites may order atezolizumab, varlilumab and cobimetinib once a patient has been enrolled to the study .
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, a "current" password, and active person registration status. 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.

8.1.4.2 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.

8.1.5 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, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.6 Useful Links and Contacts

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

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

The proposed study is an open-label, randomized phase 2 trial evaluating atezolizumab in combination with CDX-1127 (varlilumab) with or without the addition of cobimetinib in unresectable, pre-treated cholangiocarcinoma. Patients will be randomized in a 1:1 ratio to the two arms. The primary objective of the trial is to determine whether these the combination of checkpoint blockade with an immune co-stimulatory yields a clinically compelling antitumor activity (measured as overall response rates [ORR, assessed by RECIST 1.1] and progression free survival [PFS, assessed by RECIST 1.1]) and if this effect can be further amplified with the addition of MEK inhibition. Secondary endpoints include safety, overall survival (OS), immunologic correlates, and pharmacokinetics of atezolizumab and varlilumab. Objective response (OR) and PFS are co-primary endpoints.

Analysis of Co-Primary Efficacy Endpoints

Overall Response Rate (ORR):
The objective response rate 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 includes all subjects who initiated therapy. Patient who have not received a follow-up scan, and thus are not evaluable for response, will be counted as non-responders.

Progression Free Survival (PFS):
PFS is defined as the duration of time from date of randomization to time of progression or death. This analysis is intent-to-treat including all randomized patients. Patients who come off of study treatment for clinical progression without radiographic progression (i.e. clinical progression) will be coded as progression for the analysis, and the date of progression is the date of clinical progression. 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 arms using log-rank tests.

9.2 Sample Size/Accrual Rate

The study is planned for 64 evaluable subjects (32 subjects per treatment arm). The objective response rate (ORR) of BTCs treated with FOLFOX, anti-PD-1 monotherapy or anti-PDL1+MEKi is around 5%. A clinically meaningful improvement that warrants further study would be a 20% ORR. A Simon two-stage minimax design is planned for each arm. Arm specific type I error is set at 0.1 (one-sided) when evaluating the co-primary endpoints of ORR and PFS. For each arm, 18 patients will be enrolled in the first stage. If none have OR, the accrual to that arm will be terminated. If 1 or more respond, then additional 14 patients will be enrolled (for a total of 32 patients in that arm). If 4 or more patients achieve OR (12.5%) in stage 1 and stage 2 combined, the endpoint is met in that arm. The design yields at least 90% power to detect a true

response rate of at least 20%, with at least .90 probability of a negative result (no more than 3 responses if the true response rate is no more than 5%, for each of the two arms. The chance of early stopping after stage 1 in each arm is 0.4 when the true response rate is 5%.

If both arms meet the response endpoint criteria, the comparison of PFS will be performed. The median progression free survival of BTCs treated with FOLFOX, anti-PD-1 monotherapy, & anti-PDL1+MEKi is 4.0, 2.0, and 3.5 months, respectively. Randomization of 64 patients, with observation of 55 PFS events would yield 90% power to detect an HR = 0.5 (corresponding to 3.5 *vs*. 7 months median PFS in the doublet and triplet arm, respectively), at the one-sided 0.10 significance level. An observed 40% increase in median PFS for the triplet arm (approximately 1.4 months, assuming an approximately 3.5-month median PFS in the doublet arm; observed HR=0.714) would be sufficient to achieve statistical significance.

Taking into account dropout/study attrition, we anticipate screening between 70-80 patients in order to achieve 32 evaluable patients per treatment arm (N=64) with an anticipated accrual rate of 4 patients/month.

PLANNED ENROLLMENT REPORT

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	0	0	2
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	4	4	0	0	8
White	23	23	3	3	52
More Than One Race	2	2	1	1	6
Total	33	33	4	4	74

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1	0	0	2
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	4	4	0	0	8
White	20	20	1	1	42
More Than One Race	2	2	1	1	6
Total	30	30	2	2	64

9.3 Stratification Factors

Site of disease (1 level of stratification with 3 categories):
After the screening phase, eligible subjects will undergo stratified randomization according to the site of disease: 1) gallbladder cancer (GBC); 2) intrahepatic (IHC); and 3) extrahepatic cholangiocarcinoma (EHC) to ensure similar distribution of BTCs subtypes across treatment arms. 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 the sample size is small.

9.4 Analysis of Secondary Endpoints

Clinical Secondary Endpoints:

Overall survival (OS)
OS is defined as the duration of time from start of study treatment to time of death. For subjects lost to follow-up or whose vital status is unknown, every effort will be made to determine the date such subjects were last known to be alive. Such efforts may include phone calls, certified mail, and the checking of public records. Subjects who are alive or 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 known to be alive. OS will be summarized descriptively using the Kaplan-Meier method. The analysis of OS will be performed on all randomized patients, as well as all the individuals who complete at least one dose of therapy. Median OS will be reported and the associated 95% confidence interval will be estimated.

Correlative Secondary Endpoints:

Change in T-Cell populations (TILs):
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 standard deviation 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 atezolizumab and CDX-1127 (varlilumab) plus cobimetinib) than in treatment arm A (atezolizumab and CDX-1127 (varlilumab)).

Pharmacokinetics and Immunogenicity:

- Atezolizumab and CDX-1127 (varlilumab) serum concentrations will be measured using validated ELISAs. Commercially available ELISA assays for atezolizumab will be used to quantify atezolizumab in patient serum samples. For varlilumab, we will develop and validate, per FDA guidance criteria, an ELISA assay using immobilized CD27 and a labeled secondary anti-human IgG1 for detection. Similarly, for immunogenicity, we will establish screening assays for both atezolizumab and CDX-1127 (varlilumab) and perform immunodepletion in bridging assays for samples testing positive for ADAs. This will be completed within the OSUCCC PhASR lab, which is experienced with

bioanalytical assay development and validation per FDA guidance criteria, using ELISA, LC-MS and other platforms.

- Atezolizumab and CDX-1127 (varlilumab) clearance, including a time-varying rate of change, will be determined for each patient using mixed effects pharmacokinetic modeling. The methods for this will include adopting published PK models for atezolizumab as a starting point (*e.g.* Netterberg, *et al*. 2019; Stroh, *et al.* 2017) and using Bayesian estimation with the published model parameter values as priors in NONMEM (Icon, Dublin, Ireland). As no published mixed effects model for varlilumab is currently available, we will evaluate a basic 2-compartment model as a starting point and add additional structural parameters (e.g. time-varying clearance), as statistically justified. We will use the likelihood ratio test for decision-making when adding each new parameter, using the objective function value (OFV), which is chi-square distributed, and a cut-off of -3.84 change in OFV, which corresponds to a p-value of 0.05 with one degree of freedom. Once a base model is established, we will also evaluate covariates (e.g. albumin, CLcr, ADA, etc.) using forward addition/backward deletion with p = 0.01 as a cut-off for covariate retention.
- The primary assessment will be individual baseline atezolizumab clearance as a continuous variable in uni-variate and multi-variate Cox proportional hazards models for PFS. We hypothesize baseline atezolizumab clearance will be a predictor of PFS (higher baseline atezolizumab clearance will associate with shorter PFS).
- Several secondary assessments will be completed to determine associations of baseline or time-varying atezolizumab clearance with CDX-1127 (varlilumab) baseline clearance, CDX-1127 (varlilumab) time-varying clearance, and presence of cachexia. The secondary assessments will evaluate associations with PFS and OS. We hypothesize patients with high baseline atezolizumab clearance will also have high baseline CDX-1127 (varlilumab) clearance, and that the baseline clearance for both antibodies will be higher in patients with cachexia compared to patients without cachexia.

9.4.1 Analysis of Exploratory Endpoints:

<u>Tumor Microenvironment Modulation and Immunologic Response</u>
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 biliary tract cancer, 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 that will include the following comparisons with the aim of correlating these observed changes with treatment response, and toxicity:

- Baseline versus on-treatment expression of PD-L1
- Baseline versus on-treatment of immune markers quantifying ratio of CD8+ T effector cells and CD4+FoxP3+ T regulatory cells, and major histocompatibility complex (MHC) class I expression.
- Baseline versus on-treatment immune markers of T cell function and quality (see correlative studies sections above)

- Baseline versus on-treatment circulating immune cells (Tc, TH1, TH2, TH17) and cytokine profiles in peripheral blood by flow cytometry

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.

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with cobimetinib, atezolizumab, and CDX-1127 (varlilumab). 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 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.

While the combination of our proposed three study medications (or similar in-class alternatives) have not been studied in human trials, CDX-1127 (varlilumab) has been shown to be well tolerated in combination with anti-PD1, Nivolumab in patients with advanced solid tumors (NCT02335918). Additionally, the combination of cobimetinib and atezolizumab demonstrated a favorable safety profile at full doses in BTC patients (CTEP 10476). The present study will be continuously monitored for adverse events.

We will incorporate the following safety run-in and stopping rule that will be applied within each treatment group, A and B, respectively: if 2 or more “unacceptable toxicities,” at least possibly attributable to study therapy, are observed among the first 6 patients enrolled in the same treatment arm during their initial treatment cycle, we will pause the accrual in that arm and re-

evaluate safety. Accrual will be limited until the safety has been achieved in the first 6 patients in each arm, respectively.

"Unacceptable toxicities" are defined as the following treatment-related events:

- Any grade ≥2 uveitis, retinitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Recurrent grade 2 pneumonitis
- Symptomatic heart failure associated ≥10% reduction in LVEF
- Grade 3 uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction
- Any grade 3 non-skin, drug-related AE lasting >7 days, with the following exceptions:
  - Grade 3 endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 thrombocytopenia >7 days OR that is associated with bleeding requires discontinuation
    - Any liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Total bilirubin >3 × ULN
      - Concurrent AST or ALT >3 × ULN **and** total bilirubin >2 × ULN
      - In participants with liver metastasis with baseline grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasts ≥1 week
- Any grade 4 AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis. It is recommended to consult with the IND Sponsor for grade 4 amylase or lipase abnormalities.
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 lymphopenia and leukopenia.
  - Grade 4 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor.
- Any grade 5 adverse event
- Any dosing interruption lasting >6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator.
  - Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Principal Investigator must be consulted.

9.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. Each patient will be assigned one 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). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria and completed at least one dose of therapy of one the three study medications. should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

9.6 Data Safety Monitoring Board

The conduct of this study will be overseen by the ETCTN DSMB. The DSMB will be responsible for recommendations to the Principal Investigator and NCI regarding possible trial closure and/or early reporting of the study. The study team (with the exception of the study statistician) will not have access to the summary outcome data until released by the DSMB.

10. 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 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

10.1.1 CAEPRs for CTEP IND Agents

10.1.1.1 CAEPR for Atezolizumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Atezolizumab (MPDL3280A, NSC 783608)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

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.

Version 2.4, September 14, 2023[1]

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

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

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	GGT increased		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Guillain-Barre syndrome[2]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Nervous system disorders - Other (facial paresis)[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (immune-mediated myelitis)[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS])[2]	
		Skin and subcutaneous tissue disorders - Other (Exanthematous pustulosis)[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

*Denotes adverse events that are <3%.

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

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

10.1.1.3 CAEPR for Cobimetinib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Cobimetinib (RO5514041, GDC0973, NSC 781257)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 274 patients.* Below is the CAEPR for Cobimetinib (RO5514041, GDC0973).

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.

Version 2.2, March 25, 2020[1]

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Cardiac disorders - Other (left ventricular dysfunction)	
		Heart failure	
EYE DISORDERS			
	Eye disorders - Other (chorioretinopathy) [2]		
	Eye disorders - Other (eye disorders)[3]		***Eye disorders - Other (eye disorders)[3] (Gr 2)***
		Eye disorders - Other (retinal vein occlusion)[2]	
	Retinal detachment		
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		***Fever[2] (Gr 2)***
Generalized edema[4]			***Generalized edema[4] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Alkaline phosphatase increased[2]		***Alkaline phosphatase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
CPK increased			***CPK increased (Gr 2)***
	Ejection fraction decreased		
	GGT increased[2]		***GGT increased[2] (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypokalemia		
	Hyponatremia		***Hyponatremia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (new primary malignancies, cutaneous and non-cutaneous)[2]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Photosensitivity[2]		***Photosensitivity[2] (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular[5]			***Rash maculo-papular[5] (Gr 2)***
VASCULAR DISORDERS			
	Vascular disorders - Other (hemorrhage)[6]		

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

[2]Observed in combination with Vemurafenib.

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

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

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

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

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

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (cardiac ventricular thrombosis); Pericardial effusion
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Eye disorders - Other (retinal disorder); Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Dysphagia; Ileus; Lower gastrointestinal hemorrhage; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (autoimmune hepatitis); Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (cholangitis)
INFECTIONS AND INFESTATIONS - Catheter related infection; Gallbladder infection; Infections and infestations - Other (diverticulitis); Lung infection; Paronychia; Sepsis; Skin infection; Thrush; Urinary tract infection
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Electrocardiogram QT corrected interval prolonged; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression); Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Encephalopathy; Facial muscle weakness; Nervous system disorders - Other (immune-mediated encephalitis); Nervous system disorders - Other (intracranial pressure increased); Nervous system disorders - Other (7th nerve palsy); Somnolence; Syncope
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Nasal congestion; Oropharyngeal pain; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Hyperkeratosis
SURGICAL AND MEDICAL PROCEDURES - Surgical and medical procedures - Other (medical device change)
VASCULAR DISORDERS - Hypertension; Thromboembolic event

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

10.2 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 website 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 10.1) 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.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Treatment-emergent AEs: All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: *Protocols > Documents > Protocol Related Documents > Adverse Event Reporting*, and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 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.

10.3.3 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 as long as the death occurred within 30 days after the last administration of the investigational agent. 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.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** 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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[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

10.3.4 Adverse Events of Special Interest

Adverse Event Special Interest (AESIs) are a subset of events of scientific and/or medical concern specific to this protocol, for which ongoing monitoring and communication by the Investigator to the Sponsor is required.

General AESI:

- 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 and based on the following observations: - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which > 35% is direct bilirubin) - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

Suspected transmission of an infectious agent by the study treatment, as defined below - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

Atezolizumab:
AESI for Atezolizumab are:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, macrophage activating syndrome, hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Cobimetinib:

- AESI for Cobimetinib are:
- Any grade Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Significant liver toxicity: AST and/or ALT > 10 X upper limit of normal
- Symptomatic heart failure / Grade ≥ 2 left ventricular dysfunction
- Grade ≥ 3 CPK elevation or Rhabdomyolysis
- Grade ≥ 3 Diarrhea
- Grade ≥ 3 rash

Biopsy:
Adverse Events of Special Interest (AESIs) for this study are related to the biopsy component of the study. These events should be captured in Rave as they occur and should be reported expeditiously according to the table above. Four of these AESIs are not currently part of the CTCAE and must be reported in Rave/CTEP-AERS using the term: Injury, poisoning and

procedural complications - Other, specify. The AESI Terms and Grading Table below (Section 10.3.4.1) lists the AESI terms and their grading. The AESI Reporting Table (Section 10.3.4.2) provides instruction on how to record these events in Rave/CTEP-AERS.

10.3.4.1 Adverse Event Special Interest (AESI) Terms and Grading

Adverse Event Special Interest (AESI) Terms and Grading

AESI	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Definition
Biopsy-related hemorrhage	Symptomatic hematoma requiring medications	Any hematoma (symptomatic or asymptomatic) requiring unplanned observation with less than 24 hours of hospitalization	Hemorrhage requiring transfusion, radiologic, endoscopic or surgical intervention or greater than 24 hours of hospitalization	Hemorrhage with life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by bleeding related to a biopsy procedure.
Biopsy-related nerve injury	Symptomatic nerve pain or injury requiring medications	Any nerve injury requiring unplanned observation with less than 24 hours of hospitalization	Any nerve injury requiring surgical intervention or greater than 24 hours of hospitalization	Nerve injury with life-threatening consequences; urgent intervention indicated	Death	A finding of damage to a nerve related to a biopsy procedure.
Biopsy-related organ injury	Symptomatic organ pain or injury requiring medications	Any organ injury requiring unplanned observation with less than 24 hours of hospitalization	Any organ injury that requires radiologic, endoscopic or surgical intervention or greater than 24 hours of hospitalization	Organ injury with life-threatening consequences; urgent intervention indicated	Death	A finding of damage to an organ related to a biopsy procedure.
Biopsy-related anesthesia (local or moderate sedation) effects	Symptomatic anesthesia effects requiring medications	Any biopsy-related anesthesia effects requiring medical intervention for reversal of symptomatic effects and/or requiring unplanned observation with less than 24 hours of hospitalization	Any anesthesia effects requiring intervention for reversal or treatment of symptomatic effects and/or requiring greater than 24 hours of hospitalization	Anesthesia effects with life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by reactions related to the administration of local or moderate sedation given for a biopsy procedure.
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by the sensation of marked discomfort, distress or agony.
Wound infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the wound.
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an adverse local or general response from exposure to an allergen.

10.3.4.2 Adverse Event Special Interest (AESI) Reporting

Adverse Event Special Interest (AESI) Reporting

AESI Term	CTCAE term to Select	Other, specify language to record:
Pneumothorax*	Pneumothorax	N/A
Pain*	Pain	N/A
Wound infection*	Wound infection	N/A
Allergic reaction*	Allergic reaction	N/A
Biopsy-related hemorrhage**	Injury, poisoning and procedural complications - Other, specify	Biopsy-related hemorrhage
Biopsy-related nerve injury**	Injury, poisoning and procedural complications - Other, specify	Biopsy-related nerve injury
Biopsy-related organ injury**	Injury, poisoning and procedural complications - Other, specify	Biopsy-related organ injury
Biopsy-related anesthesia (local or moderate sedation) effects**	Injury, poisoning and procedural complications - Other, specify	Biopsy-related anesthesia (local or moderate sedation) effects

*Select the indicated current CTCAE Term.

**Select CTCAE term, "Injury, poisoning and procedural complications - Other, specify" and fill in the 'Specify' with the AESI term when prompted in Rave.

For example, if the subject experienced a biopsy-related hemorrhage, select Injury, poisoning and procedural complications - Other, specify and write in 'Biopsy-related hemorrhage' when prompted in Rave and/or CTEP-AERS.

10.4 Routine Adverse Event Reporting

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

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

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

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

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

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

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

10.7 Second Malignancy

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

11. STUDY CALENDAR

Informed consent is to be obtained any time prior to conducting research procedures and may be greater than 14 days before Randomization. Baseline timepoint scans, Echocardiogram (or MUGA), Eye Exam, and Pre-Treatment Biopsy are highly recommended to be done within 14 days of randomization but can be done up to a maximum of 28 days prior to randomization, if needed to accommodate scheduling limitations. Screening labs must be done within 14 days of randomization. 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. All participants receiving atezolizumab will be assessed for pulmonary signs and symptoms on physical examination as well as imaging throughout the study.

1 cycle = 28 days	Baseline		Cycle 1				Cycle 2				Cycle 3 and beyond				Progression/ End of Treatment[S]
			Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	
Visit window[A]	*-Day 14 to Randomization*	*Day 0[AA]*	*+/-2*	*+/-2*	*+/-5*		*+/-2*	*+/-2*	*+/-5*		*+/-2*	*+/-2*	*+/-5*		*+14*
Atezolizumab[B]			X	X			X	X			X	X			
CDX-1127 (varlilumab)[C]			X	X			X	X			X	X			
Cobimetinib[D]			X----------X				X----------X				X----------X				
Informed consent	X														
Demographics	X														
Medical history[E]	X														
Concomitant medications	X		X				X				X				
Physical exam[F]	X		X	X			X				X				X
Vital signs[G]	X		X	X			X	X			X	X			X
Height	X														
Weight	X		X				X				X				X
Performance status	X		X				X				X				X
CBC w/diff[H]	X		X	X			X	X			X	X			X
Serum chemistry[I]	X		X	X			X	X			X	X			X
Amylase, Lipase			X				X				X				
Coagulation (INR and aPTT)	X				X[Y]										
Thyroid function test[J]	X						X				X				X
EKG[Z]			X												
B-HCG[K]	X														
CPK	X						X[T]				X[T]				
cfDNA[L]		X													
ECHO or MUGA[U]	X				1 month after first dose, then every 3 mo on cobimetinib (see [U])										
Ophthalmologic exam[M,V]	X				Every 2 months for 1 year, then every 6 months while on cobimetinib (see [V])										
Adverse event evaluation			X	X			X	X			X	X			X[W]

1 cycle = 28 days	Baseline		Cycle 1				Cycle 2				Cycle 3 and beyond				Progression/ End of Treatment[S]
			Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	
Visit window[A]	*-Day 14 to Randomization*	*Day 0[AA]*	*+/-2*	*+/-2*	*+/-5*		*+/-2*	*+/-2*	*+/-5*		*+/-2*	*+/-2*	*+/-5*		*+14*
Tumor measurements[N]	X				Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease if possible.										X
CA 19-9[O]	X		X				X				X				X
Archival tumor sample		X													
Tumor biopsy[P]		X			X										
Peripheral blood in EDTA tubes[Q]		X			X									X[X]	X
Peripheral blood (Streck tube)[Q]		X			X										X
Peripheral blood (red top tubes for serum)[R].			X	X			X	X			X				
Medication Diary			X				X				X				

A: Longer durations to be approved by the Study Principal Investigator. Baseline timepoint scans, Echocardiogram (or MUGA), Eye Exam, and Pre-Treatment Biopsy are highly recommended to be done within 14 days of randomization but can be done up to a maximum of 28 days prior to randomization, if needed to accommodate scheduling limitations. Screening labs must be done within 14 days of randomization.

B: To be administered to both Arm A and Arm B treatment arms. Dosing as follows: atezolizumab 840 mg IV q2wks. Atezolizumab will be administered before CDX-1127 (varlilumab).

C: To be administered to both Arm A and Arm B treatment arms. Dosing as follows: CDX-1127 (varlilumab) 3mg/kg IV q2wks. Wait 30 minutes between completion of atezolizumab and subsequent start of CDX-1127.

D: For patients randomized to atezolizumab and CDX-1127 (varlilumab) plus cobimetinib *(study arm A only)*. Dosing as follows: cobimetinib 60 mg daily (21 days on/7 days off). On Days 1 and 15 of each cycle, cobimetinib should be taken before receiving atezolizumab and CDX-1127 (varlilumab). Cobimetinib should be taken in the morning at the same time every day. It can be taken with or without food. If a dose of cobimetinib is not taken within 4 hours of the scheduled dose, it should be considered missed and not taken. Resume dosing at the next scheduled dose/time. If unable to take dose prior to infusion, patient may still take that day's dose as long as it is within 4 hours of regularly scheduled time, otherwise it should be considered missed and not taken with dosing resumed at the next scheduled day/time.

E: 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.

F: 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.

G: For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), 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 only if clinically indicated.

H: Clinical hematology: CBC with differential ANC, ALC, AEC, and platelet count. Labs may be collected within a window of up to 7 days prior to Cycle 1 Day 1 dosing and up to 3 days prior to all other dosing days. Initial screening bloodwork does not need to be repeated if performed within 7 days of C1D1.

I: Serum Chemistry should include Glucose, Calcium, Sodium, Potassium, CO_2, Chloride, BUN, Creatinine, Alkaline phosphatase, Alanine amino transferase (ALT), Aspartate amino transferase (AST), Bilirubin, Albumin, GGT, Total Protein, and LDH. For patients on Arm A (i.e. receiving cobimetinib), also include Phosphorus and Magnesium. Labs may be collected within a window of up to 7 days prior to Cycle1 Day 1 dosing and up to 3 days prior to all other dosing days. Initial screening bloodwork does not need to be repeated if performed within 7 days of C1D1.

J: Baseline thyroid testing should be done only in patients with a known history of thyroid dysfunction and/or if there is a clinical concern for thyroid dysfunction at the time of study screening. Free T3/T4 should be checked reflexively if TSH is abnormal. Subsequent labs during treatment may be collected within a window of up to 3 days prior to dosing days.

K: Serum or urine pregnancy (women of childbearing potential only) is required at baseline. 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. Pregnancy tests during treatment as clinically

1 cycle = 28 days	Baseline		Cycle 1				Cycle 2				Cycle 3 and beyond				Progression/ End of Treatment[S]
			Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	Day 1	Day 15	Day 21	Day 28	
Visit window[A]	*-Day 14 to Randomization*	*Day 0[AA]*	*+/-2*	*+/-2*	*+/-5*		*+/-2*	*+/-2*	*+/-5*		*+/-2*	*+/-2*	*+/-5*		*+14*

indicated.

L: cfDNA is optional and should be collected per institional standards. Liquid biopsy recommended, if tissue-based molecular profiling was not previously performed or was performed but was inadequate for assessment of TMB and MSI/MMRd. If collected, a one time blood collection (8.5 mL) will be done at pre-treatment and sent for cfDNA analysis (NGS, blood tumor mutation burden, microsatellite instability status) on same day as collection with preference for Foundation Medicine (https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032B.pdf). Sites will be provided with cfDNA collection kits if needed (industry collection tubes). This is a standard of care test.

M: Patients with ocular symptoms occurring during study treatment should be examined by an ophthalmologist.

N: 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. For the first on-treatment scan, this should be done approximately 8 weeks from the start of treatment (not from the date of the pre-treatment baseline scan). Imaging will be repeated every 8 weeks, irrespective of dosing schedule or treatment delays. For the End of Treatment visit, scans do not need to be repeated if a scan has been performed within 8 weeks. For patients removed from study treatment for reasons other than progression, scans are to continue every 8 weeks until progression.

O: CA19-9 does not need to be repeated in the event that the screening lab draw show that the patient's tumor does not secrete CA19-9.

P: Only for subjects with tumor that in the opinion of the study treatment team is safely accessible for biopsy. See Section 5.5.2 for the order of the tumor cores to be collected. The baseline biopsy is to be done after randomization but before C1D1.

Q: Blood collection will be collected at baseline, C1D21, and Week 12 (end of Cycle 3). Pre-treatment baseline EDTA and Streck tube draws should only be drawn on enrolled patients and can be drawn anytime between time of enrollment and prior to start of treatment. These samples must be collected only Monday-Thursday and shipped overnight same day. See Section 5.1 for more details.

R: D1 of Cycles 1-6, 9, 12; pharmacokinetic and immunogenicity: pharmacokinetic blood draws will be performed pre-infusion and 30 minutes after the end of infusion of CDX-1127 (varlilumab), which will be administered after atezolizumab and D15 of Cycle 1 and 2. See Section 5.1 for more details.

S: End of Treatment evaluations will be completed no more than 30 days after the last dose of all study drugs and prior to start of next line systemic therpay.

T: Patients receiving cobimetinib *(study arm A only).* Labs during treatment may be collected within a window of up to 3 days prior to dosing days.

U: Evaluation of LV function by either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) at baseline (*all patients*), 1 month after first dose (*study arm A only*), then every 3 months while on cobimetinib (visit window +/-7 days); *(study arm A only).*

V: Ophthalmologic examination at baseline (*all patients, within 4 weeks prior to randomization*), then every 2 months for 1 year (*study arm A only*), then every 6 months while on cobimetinib (visit window +/- 14 days); *(study arm A only).* Eye exam should include retinal exam, slit lamp exam, and visual fields (preferably Goldmann Visual Field if available) for evidence of retinal pathology and other abnormalities. Alternatives to Goldmann Visual field tests such as Humphrey and Octupus visual field tests/machines are acceptable. Alternatives to checking visual acuity with Landolt chart such as ETDRS and documentation of Snellen equivalent are acceptable.

W: Adverse events will be assessed at least 30 days after the last dose of either study agent. For patients removed due to unacceptable toxicity, they will be followed until resolution of the adverse event.

X: End of Cycle 3 only (including up to prior to starting treatment on C4D1).

Y: Before the on-study biopsy.

Z: Patients receiving cobimetinib *(study arm A only).* EKG will be performed after randomization but before C1D1, at C1D15, monthly during the first 3 months, and then every 3 months thereafter or more often as clinically indicated.

AA: Day 0 = time period after randomization up until C1D1 of treatment. Baseline research blood draws (EDTA and Streck tubes) and baseline study tissue biopsies should take place during this period (after patient has completed enrollement and prior to start of therapy).

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

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) [*Eur J Ca* 45:228-247, 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.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab, cobimetinib, and CDX-1127 (varlilumab).

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.

12.1.2 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 might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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.

12.1.3 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.

12.1.4 Response Criteria

12.1.4.1 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.

12.1.4.2 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).

12.1.4.3 Evaluation of Best Overall Response

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** 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

12.1.5 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.

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.

12.1.6 Progression-Free Survival – Co-Primary Endpoint

PFS is defined as the duration of time from date of randomization to time of progression or death (whichever occurs first). This analysis is intent-to-treat including all randomized patients. Patients who come off of study treatment for clinical progression without radiographic progression (i.e. clinical progression) will be coded as progression for the analysis and the date of clinical progression is the time of progression. 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 arms using log-rank tests.

Note: For participants who receive treatment beyond disease progression 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.

12.1.7 Overall Response Rate – Co-Primary Endpoint

The objective response rate 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 includes all subjects who initiated therapy. Patient who have not received a follow-up scan, and thus are not evaluable for response, will be counted as non-responders.

12.2 Other Response Parameters

12.2.1 Overall Survival (OS)

OS is defined as the duration of time from date of randomization to time of death

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

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

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

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

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
    - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
    - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. Site staff 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

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

13.2.1 Method

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

13.2.2 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.

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).

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DPQ Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 CTEP Multicenter Guidelines

N/A

13.5 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.

13.6 Genomic Data Sharing Plan

N/A

13.7 Incidental/Secondary Findings Disclosure Procedure

N/A

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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 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

175 x $SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) × 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

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APPENDIX C PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10476

Study Drug(S): Atezolizumab
Varilimub
Cobimetinib

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX D PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at: https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_IR_Research_Biopsy_SOP.pdf.

Individual Patient Pre-Biopsy Assessment. IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

- IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

    1. Biopsy should not be done
        A. Due to safety concerns
        B. Due to lack of suitable lesion for biopsy

    2. Uncertainty about success
        A. Due to access path to lesion
        B. Due to lesion characteristics

    3. Likely successful

- Lesion characteristics to be considered
    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

APPENDIX E MEDICATION DIARY

CTEP-assigned Protocol #10476
Local Protocol # _____

PATIENT'S MEDICATION DIARY – Cobimetinib

Cycle _____ Start date _____ Agent Cobimetinib

Patient's Initials **Patient Study ID**

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of cobimetinib each day in the morning. You will take ____ 20 mg tablets.
3. You will take your dose of cobimetinib prior to your IV therapy appointments on Days 1 and 15.
4. If your dosing time is missed by greater than four hours from your regularly scheduled time, consider the dose missed and do not take it. Resume your dose at next scheduled day/time.
5. If you vomit, do not retake the cobimetinib. Take you next dose as scheduled.
6. Record the date, the number of tablets you took, and when you took them.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please return the forms to your physician when you go for your next appointment.

Day	Date	Time of morning dose	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22	X	X	X	Do Not Take
23	X	X	X	Do Not Take
24	X	X	X	Do Not Take
25	X	X	X	Do Not Take
26	X	X	X	Do Not Take
27	X	X	X	Do Not Take
28	X	X	X	Do Not Take

Physician's Office will complete this section:

1. Date patient started study drug this cycle_____
2. Date patient last took the study drug_____
3. Patient's planned daily dose_____
4. Patient's planned total dose this cycle *(i.e. 60 mg daily dose x 21 days is 1260 mg*)
5. Total number of tablets taken this cycle_____
6. Total actual dose taken this cycle _____
7. Physician/Nurse/Data Manager's Signature/Date _____

Patient's Initials/Date _____