Columbia University Irving Medical Center
Herbert Irving Comprehensive Cancer
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Herbert Irving Comprehensive
Cancer Center

COLUMBIA

Columbia University Irving Medical Center
NewYork-Presbyterian

TITLE: **MEKiAUTO:** Phase 1/2 open-label study of combination therapy with the **MEK** inhibitor, cobimetinib, **i**mmune checkpoint blockade, atezolizumab, and the **AUTO**phagy inhibitor, hydroxychloroquine in KRAS-mutated advanced malignancies.

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Funding Source:	Genentech/F. Hoffmann-La Roche Ltd. Genentech protocol # ML41472
Study Agent:	Atezolizumab Cobimetinib Hydroxychloroquine
Other Agent:	N/A
IND/IDE Status:	**IND EXEMPT**

Affiliate Institutions:

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PROTOCOL SIGNATURE PAGE

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Site Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

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Signature of Principal Investigator Date

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Site Principal Investigator Name (Print)

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Name of Institution

Protocol Synopsis

Title	**MEKiAUTO:** Phase 1/2 open label study of combination therapy with the MEK inhibitor, cobimetinib, immune checkpoint blockade, atezolizumab, and the AUTOphagy inhibitor, hydroxychloroquine in KRAS-mutated advanced malignancies.
Short Title	Cobimetinib + Atezolizumab + Hydroxychloroquine in KRAS-mutated advanced malignancies
Protocol Number	Genentech IST#: ML41472
Phase	Phase 1/2
Study Duration	18 months
Study Center(s)	Multicenter: Columbia University Medical Center, TBD
Objectives	**PRIMARY OBJECTIVES** ***Phase 1:*** To estimate the maximum tolerated dose of cobimetinib, atezolizumab, and hydroxychloroquine in KRAS-mutated advanced malignancies. ***Phase 2:*** To evaluate the preliminary efficacy based on the objective response by 16 weeks of the combination of cobimetinib, atezolizumab, and hydroxychloroquine in KRAS-mutated advanced malignancies. **SECONDARY OBJECTIVES** ***Phase 1:*** To evaluate the safety profile of the combination of cobimetinib, atezolizumab, and hydroxychloroquine in KRAS-mutated advanced malignancies. ***Phase 2:*** To evaluate the progression free and overall survival, and the safety profile of cobimetinib, atezolizumab, and hydroxychloroquine combined treatment in KRAS-mutated advanced malignancies. **Exploratory Objectives** A. Determine MEK and autophagy pathway inhibition, and CD8+ T-cell infiltration within tumor specimens. B. Perform RNA seq analysis within tumor specimens.

Number of Subjects	Phase 1: KRAS-mutated histology (N=18) Phase 2: KRAS-mutated histology pending results of phase 1 Cohort 1 – Advanced Pancreas Adenocarcinoma (N = 23-67) Cohort 2 – Advanced Colorectal Adenocarcinoma (N = 20-34) Cohort 3 – Histology Agnostic Adenocarcinoma (N = 23-56)
Study Product, Dose, Route, Regimen	Dose Level 1: Cobimetinib (40mg) orally once daily (morning) on days 1-21 of each 28-day; Hydroxychloroquine (600mg) orally twice daily on days 1-28 of each 28-day cycle Dose Level 2: Cobimetinib (40mg) orally once daily (morning) on days 1-21 of each 28-day; Hydroxychloroquine (600mg) orally twice daily on days 1-28 of each 28-day cycle; Atezolizumab 840 mg IV on Days 1 and 15 of each cycle Dose Level 3: Cobimetinib (60mg) orally once daily (morning) on days 1-21 of each 28-day; Hydroxychloroquine (600mg) orally twice daily on days 1-28 of each 28-day cycle; Atezolizumab 840 mg IV on Days 1 and 15 of each cycle 28 day cycle.
Duration of administration	Continuous 28-day cycle
Reference therapy	N/A
Statistical Methodology	The MTD will be estimated using the time to event continual reassessment method (TITE-CRM). The MTD is defined as the dose combination at which 30% of the patients experience DLT by the end of Cycle 2.

Protocol Schema:

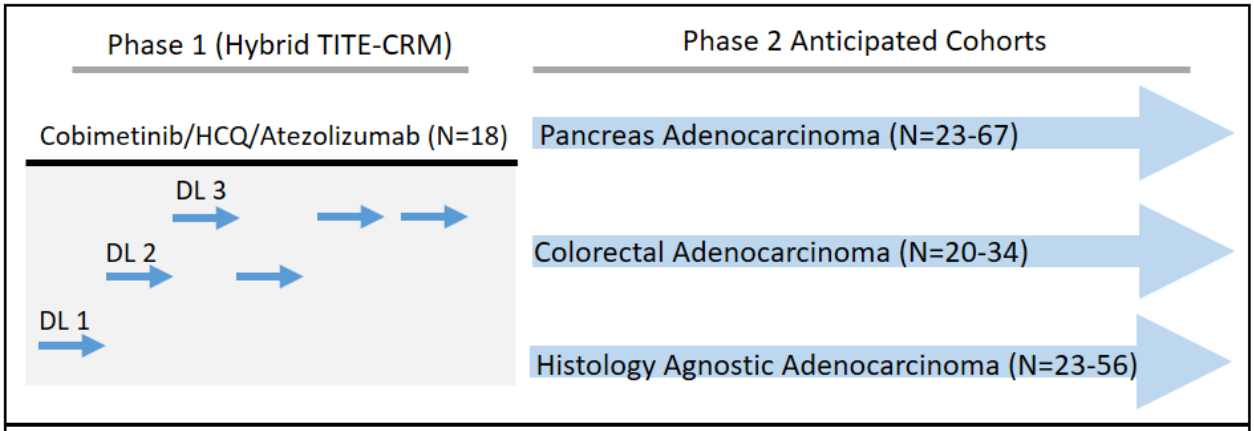

Figure. Schema of Phase 1 and 2 Clinical Trial. The phase 1 portion of the study will be conducted using a hybrid 3+3 and time-to-event continue reassessment method (h-TITE-CRM) using three dose levels. The phase 2 portion of the study will use the recommended phase 2 dose for three cohorts with *KRAS* mutation – 1. Pancreas adenocarcinoma; 2. Colorectal adenocarcinoma; and 3. Histology agnostic adenocarcinoma.

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INTRODUCTION

Pancreas adenocarcinoma (PDAC) is an aggressive cancer for which little progress has been made towards effective treatment or cure. By 2030, PDAC is projected to be the second leading cause of cancer-related death in the United States (Siegel, Miller, & Jemal, 2016). Although 'modern' combination therapies for metastatic PDA have improved survival by up to 5 months, the overall 5-year survival rate for these patients remains approximately 7%, highlighting the fact that novel therapies are desperately needed (Conroy et al., 2011; Rahib et al., 2014; Von Hoff et al., 2013). Currently, surgery remains the only curative option; however, the vast majority of patients diagnosed with PDAC either have locally advanced (~30%) or distant (~50%) disease, and are not candidates for resection (Howlader et al., 2017). Even in the those patients who receive surgery, recurrence remains high (> 60%) and median overall survival remains poor (23.6 months), despite adjuvant chemotherapy (Howlader et al., 2017; Neoptolemos et al., 2010; Neoptolemos et al., 2004; Oettle et al., 2007; Regine et al., 2008). PRODIGE 24-ACCORD, a large randomized phase 3 study compared modified FOLFIRINOX (mFOLFIRINOX) to gemcitabine monotherapy in the adjuvant setting, and demonstrated a median overall survival benefit of 54.4 months compared to 35.0 months. The median disease-free survival was 21.6 months in the mFOLFIRINOX arm compared to 12.8 months in the gemcitabine monotherapy arm (Andre et al., 2018; Conroy et al., 2018). Negative margins, smaller tumor size, and lack of lymph node involvement correlated with improved prognosis. Patients with metastasis to visceral organs, the peritoneum, or lymph nodes that are beyond the field of resection derive no benefit from surgery and are treated with systemic chemotherapy (Allison et al., 1998; Howard et al., 2006; Sohn et al., 2000).

The current standard of care for stage IV PDAC involves choosing between the two most active combination regimens, namely mFOLFIRNOX and gemcitabine/nab-paclitaxel. In 2011, Conroy et al (2018) published their landmark findings of a median survival of 11.1 months with FOLFIRINOX, compared to 6.8 months with gemcitabine alone (Conroy et al., 2011). Patients in the FOLFIRINOX group had higher rates of toxicity compared to gemcitabine. This has prompted most clinicians in the United States to favor a dose-reduced 'modified' regimen, termed "modified FOLFIRINOX." In 2013, the results of a large phase III trial, including 861 patients treated with either gemcitabine plus nab-paclitaxel or gemcitabine alone, were published (Von Hoff et al., 2013). This combination demonstrated a median overall survival of 8.5 months compared to 6.7 months for single agent gemcitabine.

Immune checkpoint inhibitors, which have garnered much enthusiasm in numerous malignancies, but have limited efficacy in PDA. Although two early-phase clinical trials investigating single agent anti-CTLA-4 and anti-PD-1 antibodies in metastatic PDA produced limited responses, data presented from a study testing durvalumab, showed a more promising disease control rate of 21% (Brahmer et al., 2012; Royal et al., 2010; Segal NH) which led to the rationale of testing combination durvalumab (anti-PD-L1) and tremilimumab (anti-CTL-4) in advanced PDA. The combination failed to demonstrate meaningful responses or extension of life (O'Reilly EM et al., 2019)

Whole-exome sequencing (WGS) studies have revealed several frequent somatic mutations in PDA, the most common of which include KRAS, TP53, CDKN2A, and SMAD4 (Dreyer, Chang, Bailey, & Biankin, 2017). The high frequency of KRAS mutations in patients with PDAC (approximately 95%) and its key role in activating the mitogen activated protein kinase (MAPK) pathway, make enzymes within this signal transduction cascade attractive targets. Recent data from a Phase 1b trial in which cobimetinib, a reversible MEK1 and 2 inhibitor, was administered in combination with atezolizumab, an anti-PD-L1 antibody, to patients with KRAS-mutated colorectal cancer demonstrated a clinical benefit in 37% of patients (Sieunarine et al., 2005). The majority of the 20% of patients who responded were MMR-P, suggesting that MEK inhibition interferes with an immunosuppressive mechanism, which allows atezolizumab to become effective. In addition, this combination led to the inhibition of phospho-ERK and increased CD8+ T-cell infiltration within the tumor, a potential correlative marker for predicting increased survival (Carstens et al., 2017). However, the randomized phase 3 (IMblaze370) study testing atezolizumab and cobimetinib versus atezolizumab or regorafenib failed to demonstrate an overall survival benefit compared to regorafenib alone (Bendell et al., 2018).

Autophagy is a catabolic process through which a cell is capable of recycling cytoplasmic proteins and organelles so that they may serve as an alternative energy source (Bryant et al., 2019; Kinsey et al., 2019). Tumor cells can induce autophagy to maintain viability and homeostasis, particularly in the oxygen-deprived tumor microenvironment. Recent data has shown that autophagy is upregulated in cancers that harbor a *kras* mutation, and that this is essential for tumor cell growth (Yang et al., 2014; S. Yang et al., 2011). Furthermore, inhibition of KRAS or other proteins in the MAP kinase pathway, with MEK and ERK inhibitors, further increase, rather than suppress, autophagic flux in *RAS*-mutant melanoma and pancreatic cancer cells (Kinsey et al., 2019; Ma et al., 2014; Sanduja et al., 2016). A preclinical study published in early 2019 demonstated the effectiveness of a strategy combining an autophagy inhibitor and a MEK inhibitor in KRAS-driven cancer (Bryant et al., 2019; Kinsey et al., 2019).

Here we propose a phase I/IIb study to investigate the novel combination of the autophagy inhibitor, hydroxychloroquine, with a MEK inibitor, cobimentinib, and an immune checkpoint inhibitor atezolizumab.

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312/812 and International Conference on Harmonization guidelines), applicable government regulations, and Columbia University Medical Center institutional research policies and procedures.

1. STUDY OBJECTIVES

The overall objective of this study is to investigate the safety and preliminary efficacy of combination therapy with cobimetinib and hydroxychloroquine, with or without atezolizumab in patients with KRAS-mutated advanced malignancies. Given that the pre-clinical and clinical benefit from this combination is from within PDAC animal models and human subjects with PDAC and duodenal cancer, we will include atleast 12 of the 18 evaluable subjects from PDAC

and/or colorectal malignancies. The phase 2 portion of the study will be ammended after preliminary safety and efficacy results from phase 1 and other ongoing clinical trials have been analyzed and a summary encorporated within the protocol as an amendment including a rationale of the cohorts to be tested. The amendment will be submitted to the Scientfic Review Committee at CUIMC for approval prior to activation of phase 2 portion of the study.

Specific objectives are:

Phase 1:

Primary: To estimate the maximum tolerated dose (MTD) of the combination of cobimetinib, atezolizumab, and hydroxychloroquine in KRAS-mutated advanced malignancies.

Secondary: To evaluate the safety profile of the combination of cobimetinib, atezolizumab, and hydroxychloroquine in KRAS-mutated advanced malignancies.

Phase 2:

Primary: To evaluate preliminary efficacy based on the objective response by 16 weeks of the combination cobimetinib, atezolizumab, and hydroxychloroquine treatment in KRAS-mutated advanced malignancies.

Secondary: To evaluate the progression-free time and overall survival and safety in patients treated with cobimetinib, atezolizumab, and hydroxychloroquine combined treatment in KRAS-mutated advanced malignancies.

Exploratory analysis objectives:

- Determine MEK and autophagy pathway inhibition and CD8+ T-cell infiltration within tumor specimens.
- Perform RNA seq analysis within tumor specimens.

2. BACKGROUND

2.1 Rationale for MEK1/2 and autophagy inhibitor combination therapy

Autophagy is a catabolic process which involves degradation of cytoplasmic proteins and organelles so that they may be recycled and serve as an alternative energy sources for a cell (Fig. 1; (Bryant et al., 2019; Kinsey et al., 2019). Tumor cells, in a manner similar to that of healthy cells that have been stressed, can induce autophagy to maintain viability and homeostasis. The hypoxic tumor microenvironment of many solid tumors results in an increase in autophagy and produces an aggressive phenotype capable of resisting current anticancer therapies (Janji et al., 2016).

The RAF-MEK-ERK-MAP kinase pathway plays a key role in cell replication, differentiation, invasion, tumor pathogenesis, and regulation of apoptosis (Downward, 2003; Roberts & Der, 2007). KRAS is a critical switch in this pathway, and when mutated, constitutively propagates signals to the the nucleus driving tumorogenesis. So-called "driver" mutations in this gene have been desribed in over 95% of pancreatic cancer, 25-52% of colorectal cancer, and 15-35% of non-small cell lung cancers (Bettegowda et al., 2014; Chapman, Sun, Ruestow, Cowan, & Madl, 2016; Dreyer et al., 2017; Tsilimigras et al., 2018). Although the development of KRAS inhibitors has been a focus of research for decades, no efficacious pharmacologic agent has been reported to date, and downstream inhibition of the pathway by targeting MEK alone has not resulted in any meaningful clinical benefit (Humphris et al., 2017; Infante et al., 2014).

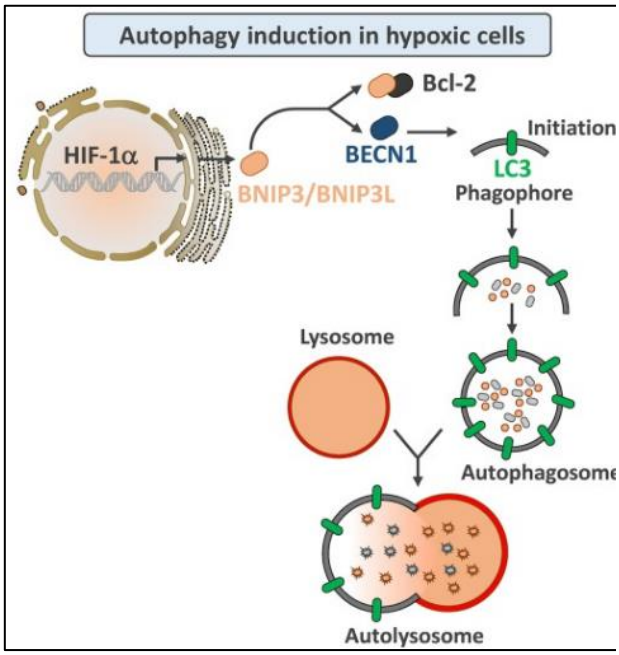

Figure 1. Autophagy induction in hypoxic cells.
Under hypoxic conditions, stabilization of HIF-1α promotes its translocation to the nucleus and leads to a rapid induction of the BH3-only proteins (BNIP3 and BNIP3L) through its binding to the hypoxia response element in the promoter of BNIP3. The induction of BNIP3 and BNIP3L displaces Beclin1 from Bcl-2, leading to the induction of autophagy (Janji et al., 2016).

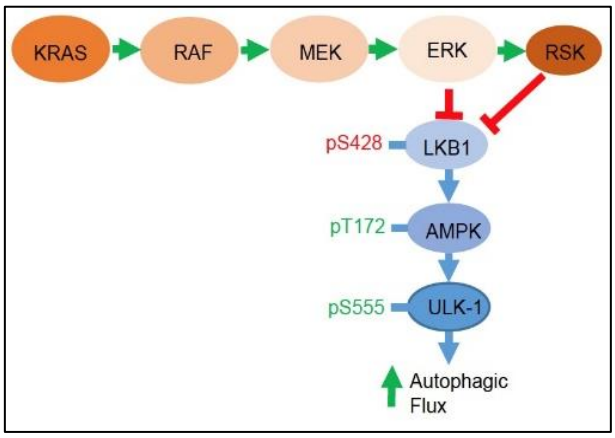

Figure 2. Proposed signal transduction cascade.
Signal transduction cascade of the proposed mechanism of action through which MAP kinase signaling may promote autophagic flux in pancreatic cancer cells (Kinsey et al., 2019)

Emerging data demonstrates that autophagy is upregulated in KRAS-mutant cancers and that it is critical for tumor cell growth (Yang et al., 2014; S. Yang et al., 2011). Interestingly, inhibition of KRAS or other proteins in the MAP kinase pathway with MEK and ERK inhibitors further increases, rather than decreases, autophagic flux in *RAS*-mutant melanoma and pancreatic cancer cells (Kinsey et al., 2019; Ma et al., 2014; Sanduja et al., 2016). The proposed mechanism is thought to be related to an increase in the LKB1 → AMPK → ULK1/ATG1 signaling axis (Fig. 2). Based on this premise, blocking MEK-inhibition driven autophagy presents a novel strategy to target RAS-driven cancer.

Hydroxychloroquine is one of the best studied autophagy inhibitors but has demonstrated limited activity as a single agent (Boone et al., 2015; Wolpin et al., 2014). Recently, several studies have shown that inhibition of MEK1/2 and autophagy (with hydroxychloroquine) promotes striking synergy and regression of xenografted patient-derived PDAC tumors in mice, NRAS-mutant melanoma, and BRAF-mutant CRC (Fig. 3) (Bryant et al., 2019; Kinsey et al., 2019).

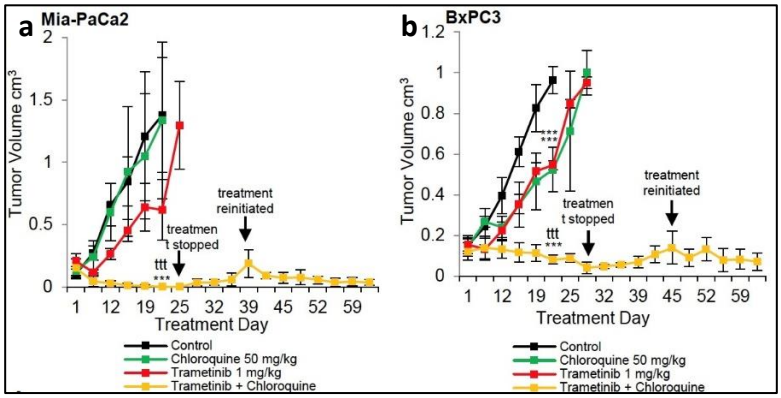

Figure 3. Change in tumor volume over 60 days of treatment.
Change in tumor volume over approximately 60 days in mice xenografted with either Mia-PaCa2 (a) or BxPC3 (b) cells and treated with: (1) vehicle (Control); (2) trametinib (1 mg/kg); (3) chloroquine (50 mg/kg); or (4) the combination of both agents at the aforementioned doses were assessed as indicated. Mia-PaCa2: control, $n = 5$, trametinib, $n = 6$, chloroquine, $n = 5$, combination of both agents, $n = 4$. BxPC3: $n = 6$ for all treatment groups. Center values are the mean; statistical testing was performed by two-sided *t*-test; $^{***}P < 0.001$ versus control; $^{ttt}P < 0.001$ versus trametinib. Error bars represent SD (Kinsey et al., 2019)

2.2 Rationale for the addition of immune-checkpoint blockade to combination MEK1/2 and autophagy inhibitor therapy.

Increased mutational burden within tumor DNA is hypothesized to lead to increased expression of antigenic peptides which drive the anti-tumor therapeutic immune response unleashed by immune checkpoint inhibitors (Azuma et al., 2014; Rizvi et al., 2015; Snyder et al., 2014). Several recently published studies have demonstrated synergistic effects of combination chemo-immunotherapy and targeted-immunotherapy in both non-small cell lung cancer and hepatocellular carcinoma (Gandhi et al., 2018; Ikeda et al., 2018). The mechanism by which combination therapies may synergize with immune check point blockade is currently unknown but exposure of neoantigens is

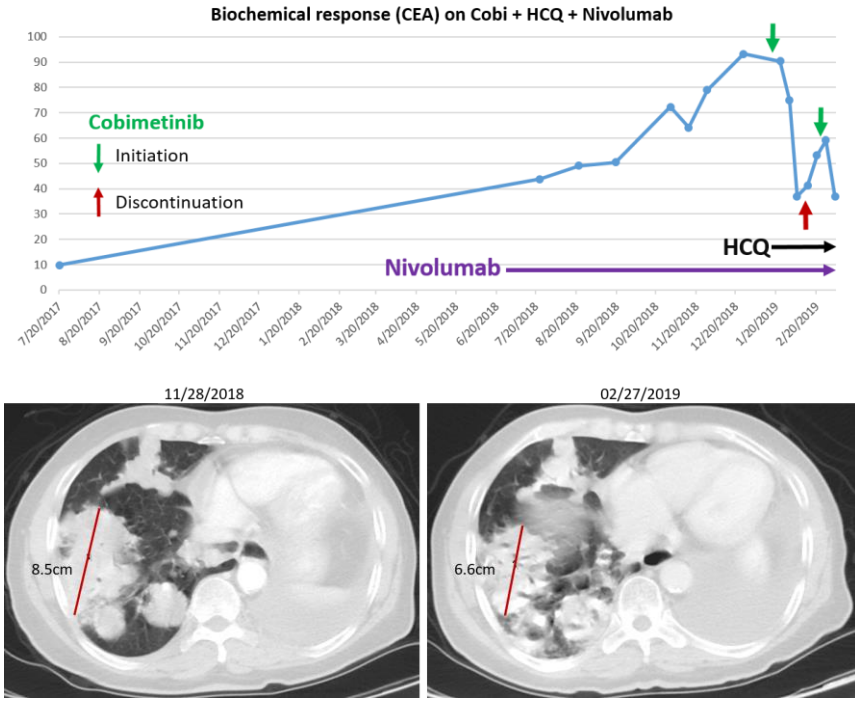

Figure 4. Change in plasma carcinoembryonic antigen and tomography images
(a) Change in plasma carcinoembryonic antigen (CEA) in a patient with recurrent stage IV KRAS G12R mutated duodenal adenocarcioma treated with hydroxychloroquine (HCQ) in combination with cobimetinib and nivolumab. (b) Computed tomography depicting decrease in size of large right lung mass following the initiation of treatment. Manji GA, unpublished.

one of the leading hypotheses. In addition, hydroxychloroquine has been shown to enhance neo-antigen presentation and antigen cross-presentation via MHC class I and thus promote antitumor immune responses (Liu et al., 2018). Xenografted tumors from mice treated with MEK and autophagy inhibition demonstrated increased CD8+ T-cell infiltration. Furthermore, in preliminary results, addition of immune check point blockade to this combination resulted in further tumor response (Kinsey et al. unpublished data). Using this rationale, we administered hydroxycholorquine (HCQ) in combination with cobimetinib to a 63 year old male with recurrent stage IV KRAS G12R-mutated duodenal adenocarcioma with bilateral pulmonary metastasis who had progresed on all standard of care therapy. Mutation profiling of the tumor identified a number of mutations which would be consistent with that of a high mutation burden due to which Nivolumab was initiated. He next progressed on Nivolumab and required 4 to 6 liters of supplemental oxygen, but within one week of addition of HCQ and cobimetinib to nivolumab, his performance status improved, oxygen requirement resolved, and plasma carcinoembryonic antigen (CEA) declined from 90.5 to 74.9. CEA continued to decline the following week to 37.5 (Fig. 4a). He remained on treatment for six weeks and has tolerated therapy well, except for Grade 2 anorexia and Grade 1 diarrhea. CT of the chest four weeks after initiation of therapy identified pulmonary nodules which decreased in size with a response rate of -13% (Fig. 4b). Collectively, the preclinial and clinical data sumarized above justifies testing this combination in subjects with KRAS-mutated advanced adenocarcinoma as proposed in this clinical trial (GA Manji, unpublished data, Columbia University).

2.3 Current treatment outcomes in patients with *KRAS*-mutant cancers.

Of all the oncogenes described in human cancer, *RAS* gene family members are the most prevalent, with approximately 20% of all tumors having undergone an activating *RAS* mutation (Downward,

2003). There are three members within this family, namely *HRAS, KRAS* and *NRAS,* and all have been identified in a multitude of malignancies with various degrees of prevalence. *RAS* encodes a small GTPase that regulates normal cellular proliferation, which, when mutated, leads to deregulation of tumor-cell growth, cell death, and tumor invasion (Shields, Pruitt, McFall, Shaub, & Der, 2000).

Pancreas Adenocarcinoma

Whole exome sequencing (WES) studies have revealed several frequent somatic mutations in PDAC, the most common of which is *KRAS* which is seen in over 90% of patients (Dreyer et al., 2017). The high frequency of *KRAS* mutations and its key role in PDAC pathogenesis make the pathway an attractive target. Again, we have seen limited success with this approach, and currently chemotherapy remains the mainstay of treatment in this aggressive disease. In general, pancreatic cancer patients tend to do poorly after progression on first-line therapy. The only FDA approved second-line regimen consists of fluorouracil, folinic acid, combined with nano-liposomal irinotecan (Garrido et al., 2017). In patients treated with this regimen the median overall survival is 6.1 months compared to 4.2 months with fluorouracil and folinic acid. Progression free survival (PFS) was improved with addition of nano-liposomal irinotecan with 3.1 months compared to 1.5 months. Below we summarize some of the clinical outcomes in PDA which have resulted in either monotherapy or combination therapy targeting – PD-1, PD-L1, CTLA-4, autophagy, and/or the mitogen-activated protein kinase pathway.

- **Immunotherapy** –

  Inhibition of programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), or anticytotoxic T-lymphocyte ‑ associated antigen 4 (CTLA-4) have failed to result in appreciable responses in metastatic pancreas adenocarcinoma. Given that two of 29 subjects from a phase 1 expansion study with durvalumab (anti-PD-L1) monotherapy showed a partial response, a randomized study evaluating durvalumab in combination with tremilimumab (anti-CTLA-4) was conducted (Segal, et al. 2014) . Unfortunately, combination therapy only resulted in a 3.1% response rate compared to no responses observed in the durvalumab arm. Both combination or monotherapy treatments failed to extent survival (3.1m versus 3.6m) (O'Reilly, et al. 2019). Taken together, these studies indicate that in a majority of PDAC patients, immunotherapy remains ineffective, despite suggestions that immune evasive mechanisms may contribute to PDAC being resistant to therapy.

- **Autophagy** –

  Autophagy is a regulated process used by cells to recycle macromolecules and organelles and is used by some cancers for cell propagation. Hydroxychloroquine (HCQ) inhibits the fusion of the autophagosome to the lysosome, a critical step in autophagy. HCQ was tested in pretreated metastatic pancreas adenocarcinoma patients as monotherapy (up to 600mg twice daily), but failed to show an efficacy signal (Wolpin, et al. 2014). Although the autophagy pathway is active in PDAC, the preclinical studies described in sections 2.1 implicate that

autophagy is used to circumvent MEK inhibition to allow tumor growth and not the primary driver pathway for cell replication. Similarly, combination gemcitabine/nab-paclitaxel and hydroxychloroquine was tested in a randomized phase 2 study in advanced pancreas adenocarcinoma. Although the combination failed to prolong overall survival at 12 months compared to chemotherapy alone (Karasic et al. 2019), response rate was significantly higher with gemcitabine/nab-paclitaxel/HCQ compared to gemcitabine/nab-paclitaxel alone (38.2% versus 21.1%; *P*=0.047), suggestive of an efficacy signal which is not durable. Consistent with this finding, gemcitabine/nab-paclitaxel in combination with HCQ in the neoadjuvant setting demonstrated improvement in pathological responses (Miller-Ocuin et al. 2017). Similarly, combination of HCQ with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and bevacizumab failed to prolong survival but resulted in an impressive response rate of 68%, including 11% complete response (O'Hara eta al. 2017).

- **Mitogen extracellular signal-related kinase Inhibition –**

The mitogen-activated protein kinase (MAPK) pathway is active in most pancreas cancer tumors given that an activated mutation within *KRAS* is identified in tumors from nearly 95% of patients. Trametenib, a reversible MEK1/2 inhibitor in combination with gemcitabine resulted in no progression free survival or overall survival (Infante et al. 2014). Although median overall survival was 8.4m compared to 6.7m with gemcitabine alone, the improvement was not durable.

Colorectal Adenocarcinoma

In colon cancer, the frequency of *KRAS* mutations is over 45% and its presence is of clinical importance as it precludes the administration of epidermal growth factor receptor (EGFR)-directed therapies (Downward, 2003). Patients with colon cancer, regardless of having a *RAS* mutation, have several options after progressing on second-line therapy. For those patients who have progressed on fluoropyrpyrimidine-based combination therapy, with irinotecan and oxaliplatin, the most commonly used subsequent-line regimens in the United States include Trifluridine/Tipiracil (TAS-102), Regorafenib, immunotherapy for those with mismatch repair deficient (dMMR) disease or microsatellite instability (MSI-H). The phase 3 CORRECT study demonstrated a median overall survival (mOS) of 8.8 months [95% CI 7.3-9.8] in patients who received regorafenib versus 6.3 months [4.8-7.6] in those receiving placebo (Li et al., 2015) and a PFS benefit of 1.9 months compared to 1.7 months. Similarly, the phase 3 TERRA study showed a mOS of 7.8 months [95% CI, 7.1 to 8.8 months] with TAS-102 versus 7.1 months [95% CI, 5.9 to 8.2 months] in those receiving placebo (Xu et al., 2018) with a PFS benefit of 2.0 months compared to 1.8 months. In an open-label, phase II trial by Overman et al., which provided nivolumab and ipilimumab to patients with dMMR/MSI-H metastatic colorectal cancer who had disease progression or were intolerant to ≥ one prior systemic treatment that included a fluoropyrimidine and oxaliplatin or irinotecan showed a significant response rate of 55% and mOS that had not reached at median follow-up of 13.4 months. Unfortunately, dMMR/MSI-H patients

only comprise about 4% of patients with metastatic colon cancer and therefore few patients are eligible for this combination. Attempts to treat patient whose tumors harbor *KRAS* mutation with either Trametinib or Selumetinib, oral selective inhibitors of *MEK1/2* kinases, have yet to yield positive results (Gandara et al., 2017; Janne, Mann, & Ghiorghiu, 2016).

Nonsmall Cell Lung Cancer (NSCLC)

NSCLC patients with KRAS mutation are treated similarly to those without the mutation. Recent advances in NSCLC have overhauled treatment paradigms to include immunotherapy in the first-line setting. This change in first line standard of care therapy has made ordering of subsequent lines of therapy, challenging. In patients who progress following first-line therapy, it is generally accepted that single agent chemotherapy, such as docetaxel or pemetrexed, or combination therapy, such as ramicurimab and docetaexl, or finally, immunotherapy, if it had not been used prior, be attempted. Docetaxel has been compared to pemetrexed in the second-line setting and no difference in the mOS was observed (8.3 versus 7.9 months (*P* = not significant) for pemetrexed and docetaxel, respectively) (Hanna et al., 2004). The REVEL study demonstrated a mOS of 10.5 months in patients allocated to ramucirumab plus docetaxel, versus 9.1 months for patients who received placebo plus docetaxel in the second line setting (hazard ratio 0.86, 95% CI 0.75–0.98; p=0.023) (Garon et al., 2014). Several studies have looked into immunotherapy in the second and third line settings. The KEYNOTE-010 trial compared pembrolizumab to docetaxel in patients who were previously treated and found a mOS of 12.7 months with pembrolizumab vs 8.5 months with docetaxel (Herbst et al., 2016). Atezolizumab was evaluated in patients with NSCLC who had received one or more lines of prior chemotherapy in the phase III OAK trial. The investigators noted a median overall survival of 15.7 months with atezolizumab versus 10.3 months with docetaxel; HR 0·74 [95% CI 0.58–0.93]; p=0.0102) (Rittmeyer et al., 2017).

3. INVESTIGATIONAL AGENT

3.1 Atezolizumab

3.1.1 Background

Atezolizumab (TECENTRIQ®), formerly known as MPDL3280A, is a humanized IgG1 monoclonal antibody (MAb) consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids), and is produced in Chinese hamster ovary cells. The antibody blocks interaction of PD-L1 to PD-1 receptor and CD80 (B7.1), which are inhibitory receptors on immune cells, including T cells. This inhibition is thought to enhance tumor specific T-cell function through enhanced priming, expansion, and effector function (Okazaki and Honjo 2007). Hence, disrupting this pathway with atezolizumab has been effective in various tumor subtypes. Atezolizumab lacks Fc-effector function, as it is engineered to be a non-glycosylated antibody, and hence does not function in antibody-dependent cell-mediated cytotoxicity or antibody-mediated clearance of activated effector T cells. Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab shows anti-tumor activity in both pre-clinical

models and in patients with cancer. It is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent and in combination with chemotherapy in multiple tumor histologies. Studies demonstrate a clinical benefit in triple negative breast cancer (Schmid et al., 2018), extensive stage small cell lung cancer (Horn et al., 2018), and non-small cell lung cancer (Socinski et al., 2018). Refer to the most current version of Atezolizumab Investigator's Brochure for details on non-clinical and clinical studies.

3.1.2 Rationale for Treatment with Atezolizumab

Encouraging clinical data emerging in the field of tumor immunotherapy has demonstrated that therapies focused on enhancing T-cell responses against cancer can result in significant clinical benefit to patients across a broad array of advanced malignancies (Hodi et al., 2010; Kantoff et al., 2010). The PD-L1 pathway serves as an immune checkpoint to dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation; expression is sustained in states of chronic stimulation (Blank, Gajewski, & Mackensen, 2005; Keir, Butte, Freeman, & Sharpe, 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte, Keir, Phamduy, Sharpe, & Freeman, 2007; J. Yang et al., 2011). Overexpression of PD-L1 on tumor cells may impede anti-tumor immunity, resulting in immune evasion (Blank & Mackensen, 2007). Therefore, interrupting the PD-L1 pathway is an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including non-small cell lung cancer (NSCLC), urothelial carcinoma, renal cell carcinoma (RCC), melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see most current version of Atezolizumab Investigator's Brochure for detailed efficacy results). Atezolizumab has been generally well tolerated. Adverse events with potentially immune-related causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see most current version of Atezolizumab Investigator's Brochure for detailed safety results).

3.1.3 Pharmacology of Atezolizumab

Atezolizumab is a humanized antibody containing heavy chain VHIII and light chain Vκl subgroup sequences. The antibody lacks the N-linked oligosaccharides due to an asparagine to alanine substitution at position 298 of each heavy chain, resulting in a non-glycosylated antibody.

Atezolizumab is produced in Chinese hamster ovary (CHO) cells and is provided in 2-mL (Formulation F01 or early Phase I/II material) and 20-mL (Formulation F03 or late Phase I/II and Phase III material) glass vials. The diluent used with Formulation F01 is provided in 50-mL glass vials. The respective protein concentrations for Formulations F01 and F03 are 125 mg/mL and 60

mg/mL, respectively. Atezolizumab (F01 and F03) and diluent are in a solution containing histidine acetate, sucrose, and polysorbate 20.

3.1.4 Clinical Data to Date: Atezolizumab

For most up to date information on clinical data available, refer to current version of Institutional Brochure.

3.1.4.1 Effect of Atezolizumab in Humans

As of the August 2018 Investigator's Brochure (version 13), clinical data on atezolizumab as a single agent or in combination with chemotherapy or targeted agents are available from more than 20 studies. Atezolizumab is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma who fit the following criteria: 1) are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells covering ≥ 5% of the tumor area), as determined by a US Food and Drug Administration (FDA)-approved test; or 2) are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status; or 3) have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. Atezolizumab is also approved for the treatment of previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC).

Pharmacokinetic, exposure-safety, and exposure-efficacy data analysis, as reported in the Atezolizumab Investigator's (version 13) identified that age, body weight, gender, albumin levels, tumor burden, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status had no clinically relevant effect. Positive anti-drug antibody (ADA) status against atezolizumab led to approximately 13% reduction in overall exposure. The effect of hepatic impairment (bilirubin or aspartate aminotransferase > upper limit of normal) on the pharmacokinetics of atezolizumab is unknown.

3.1.4.2 Effect of atezolizumab in combination with cobimetinib

The randomized phase 3 IMblaze370 study tested combination atezolizumab and cobimetinib versus atezolizumab or regorafenib alone in patients with advanced colorectal cancer who had progressed on or were intolerant of two lines of therapy. Of those treated with atezolizumab and cobimetinib, 61% experienced Grade 3/4 adverse events compared to 58% who were treated with regorafenib, an approved drug for metastatic colorectal adenocarcinoma. Diarrhea (11%), anemia (6%), increased blood creatine phosphokinase (7%), and fatigue (4%) were the most commonly observed all-cause Grade 3 – 4 toxicities in subjects treated with cobimetinib and atezolizumab (SAEs were reported in 40% subjects receiving combination therapy). Of the AEs, 26% of subjects experienced serious treatment-related AEs, 21% stopped treatment, and 61% required dose interruption or modification (Eng et al., 2019).

3.1.5 Tolerability profile during combination treatment

In studies investigating the combination of atezolizumab with other anti-cancer agents, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Fatigue, decreased appetite, nausea and cough were adverse events reported in more than 10% of patients treated with atezolizumab monotherapy and in combination therapy. Through appropriate routine evaluations, investigational workup, and early mitigations, such as management guidelines, the majority of patients were able to continue atezolizumab therapy (see most current version of Atezolizumab Investigator's Brochure for detailed safety results).

3.2 Cobimetinib

3.2.1 Background

Cobimetinib is a potent and highly selective small molecule inhibitor for MEK1 and MEK2, which are known key players of the RAS/RAF pathway (see Section 2.0). Inhibition of MEK1 and MEK2 results in inhibition of ERK1/2 phosphorylation and thus decreased cell proliferation. Cobimetinib is a substrate of CYP3A4 and UGT2B7 and an inhibitor of isozymes CYP2D6 and CYP3A4. 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.

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.

3.2.2 Toxicology

The nonclinical toxicity of cobimetinib was characterized in single-dose and repeat-dose studies in rats and dogs, a 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 assays) 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.

3.2.3 Clinical Data

Cobimetinib has been approved in the United States for the treatment of advanced melanoma in tumors that encode a mutation in *BRAF* V600E or V600K in combination with vemurafinib. Cobimetinib is generally well tolerated, but common AEs include fatigue, rash, diarrhea, nausea, emesis, edema, ophthalmological disorders, and abdominal pain. For the most up to date information on clinical data, refer to current version of Institutional Brochure. Clinical information regarding combination cobimetinib and hydroxychloroquine is listed above (Section 2.2).

3.3 Hydroxychloroquine

3.3.1 Background

Hydroxychloroquine sulfate is a colorless crystalline solid, soluble in water to at least 20%. Chemically, the drug is 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino] ethanol sulfate (1:1). The drug possesses antimalarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis. The precise mechanism of action is not known. It is indicated for the suppressive treatment and treatment of acute attacks of malaria due to *Plasmodium* vivax, *P.* malariae, *P.* ovale, and susceptible strains of *P.* falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis. The detailed mechanism by which hydroxychloroquine inhibits autophagy is currently unknown.

3.3.2 Clinical Data to Date

Hydroxychloroquine sulfate (HCQ) is supplied in 200mg tablets, and when supplied to healthy males resulted in peak blood concentration of 129.6ng/mL in 3.26 hours. The half-life of HCQ is 2963 hours (123.5 days). Renal clearance after 6 months of chronic exposure did not appear to change renal clearance. Dose adjust is not required for patients with renal impairment. In patients with rheumatoid arthritis (RA) there was large variability in the absorption of the drug.

3.3.3 Contraindications

Hydroxychloroquine is contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds.

Adverse events noted from hydroxychloroquine include:

Ocular -

Irreversible retinal damage has been observed in some patients who have received hydroxychloroquine. Risk of this AE increases with dosage greater than 6.5mg/kg of actual body weight, use of durations greater than five years, subnormal glomerular filtration, use of some concomitant drug products, such as tamoxifen citrate, and concurrent macular disease.

Cardiotoxicity and QT Prolongation –

Postmarketing cases of lifethreatening and fatal cardiomyopathy have been reported. Patients may present with atrioventricular block, pulmonary hypertension, sick sinus syndrome, or cardiac complications. ECG findings may include atrioventricular right or left bundle branch block.

Worsening of psoriasis and porphyria –

Use of hydroxychloroquine in patients with this condition may precipitate a severe attack.

Proximal Myopathy and Neuropathy –

Progressive muscle weakness and proximal muscle group atrophy have been reported, including depressed tendon reflexes and abnormal nerve conduction.

Neuropsychiatric events, including suicidality –

Suicidal behavior has been rarely reported in patients treated with hydroxychloroquine.

Hypoglycemia –

Hydroxychloroquine has been reported to cause severe hypoglycemia, including loss of consciousness, which can be life threatening in patients who may or may not be on anti-diabetic therapy.

Other –

Hydroxychloroquine should be used in caution with patients who have compromised hepatic or renal function. Blood counts should be monitored to ensure no myelosuppression. Dermatitis has been reported with the use of hydroxychloroquine.

Drug Interactions –

Digoxin, insulin or other antidiabetics, drugs that prolong QT interval, antiepileptics, methotrexate, cyclosporine, praziquantel, antacids, cimetidine, and ampicillin have significant interactions with hydroxychloroquine.

3.4 Other Agent(s)

N/A

4. STUDY DESIGN

4.1 General Design

4.1.1 Phase 1

The objective of this study is to determine the maximum tolerated dose (MTD) of the combination of cobimetinib, atezolizumab, and hydroxychloroquine. We will evaluate three dose combinations. Patients will be treated with combination therapy at the designated dose levels depicted in Table 1, based on a 28 day cycle (Section 7.3). The MTD is defined as the dose associated with a target probability of dose limiting toxicity of 0.30. The primary endpoint is DLT in the first cycle of treatment.

Given that cobimetinib is approved at a dose of 60 mg orally daily and hydroxychloroquine was well tolerated at 600 mg orally twice daily, we feel that the combination will be well tolerated (Wolpin et al., 2014). Cobimetinib and atezolizumab were tested in advanced colorectal cancer in IMblaze370, a large randomized phase 3 clinical trial (Eng et al., 2019) with proportion of patients experiencing grade 3 and over adverse events similar to those who received the FDA approved Regorafenib. Subjects will receive cobimetinib in cohort 1 and 2 at a lower dose (40mg oral daily) compared to that tested in IMblaze370 (60mg oral daily). Given that, other than ocular and hepatic toxicity, hydroxychloroquine has little to no overlapping adverse events with cobimetinib and atezolizumab, we do not anticipate significant toxicities with this combination at the doses being tested. Ocular toxicities with hydroxychloroquine are observed at high cumulative doses and will be monitored by required scheduled ophthalmological evaluations throughout the study period. We will initiate Phase 1 at dose level 1 using a combined 3+4 and time-to-event continual reassessment method (TITE-CRM). Table 1. Cohort dose levels.

Patient No.	Dose Level	Hydroxychloroquine (mg) (oral; 1200mg/day; Days 1-28)	Cobimetinib (mg) (oral; 40-60mg/day; Days 1-21)	Atezolizumab (mg) (IV; 840mg every two weeks)
1, 2, 3	**1**	**600mg twice per day**	**40mg**	
4, 5, 6	**2**	**600mg twice per day**	**40mg**	**840mg**
7, 8, 9 10-18	**3**	**600mg twice per day TITE-CRM**	**60mg**	**840mg**

Phase I Statistical Considerations

The MTD will be estimated using a two-stage time to event continual reassessment method (TITE-CRM), whereby in the first stage patients will be assigned to 3-patient cohorts (see table below) in the absence of DLT. However, once a DLT is observed, we will initiate the second stage and patients will be assigned using the TITE-CRM. The initial design for the two stage was obtained using the method by Jia, et al (Jia, Ivanova, & Lee, 2017).

Table 2. Selection probabilities and average expected number of patients assigned to each dose based on the two stage TITE-CRM (N=18)

Doses Level		1	2	3
Scenario 1	**DLT rate**	30%	45%	55%
	P(Selection)	74%	23%	4%
	Average Number Assigned	11	4	3

Scenario 2	**DLT rate**	15%	30%	45%
	P(Selection)	24%	53%	23%
	Average Number Assigned	6	6	6
Scenario 3	**DLT rate**	5%	15%	30%
	P(Selection)	1%	25%	74%
	Average Number Assigned	2	5	11

The advantage of the TITE-CRM is that it uses the patient's partial information before a complete follow-up is achieved. As a result, we can conduct the trial in a continuous fashion without having patients be turned away due to waiting time. The TITE-CRM will use an empirical dose-toxicity model, with a sample size of 18. The prior distribution of the model parameter is assumed to be normal with a mean of 0 and a variance of 1.34. The dose-toxicity model is calibrated such that the eventual dose yields between 18% and 32% DLT (Cheung & Chappell, 2002; Lee & Ying Kuen, 2009) and good operating characteristics across a wide range of potential scenarios of toxicity profiles. Given that the majority of the toxicities for the cobimetinib and atezolizumab trial occurred in the first cycle of treatment, the proposed toxicity evaluation period is 4 weeks. In the first stage, each cohort will be followed for the entire 4 weeks in the absence of a DLT. Once a DLT is observed, we will impose a minimum of 1 week of observation between patients in the second stage of the design. We do not allow for dose skipping during dose escalation or escalation immediately after a dose limiting toxicity. **Patients who do not complete 80% of dosing due to reasons other than treatment-related toxicity (e.g. non-compliance) will need to be replaced. Moreover, patients who discontinue due to reasons other than treatment-related toxicity (i.e. progression or death) prior to completing 4 weeks of therapy without having experienced a DLT will be considered not evaluable and be replaced.** Partial toxicity information from subjects that are greater than 80% compliant may be included for dose assignments and will continue to be used for future dose assignments unless the patient is not evaluable and/or discontinues prior to the 4 week DLT evaluation. To evaluate the performance of the method, 2000 simulations under these scenarios of toxicity profiles were done. The operating characteristics of our design under these scenarios are displayed in Table 2. Based on these simulation results, the 18-patient design selects the correct MTD with probabilities over 53% under all possible scenarios. These simulations assume that the patients arrive at a rate of 4 patients every 4 weeks (i.e., a patient every week) which is our full toxicity evaluation window, and that a DLT occurs randomly and uniformly

within the observation window. Moreover, based on the various simulation scenarios, we expect

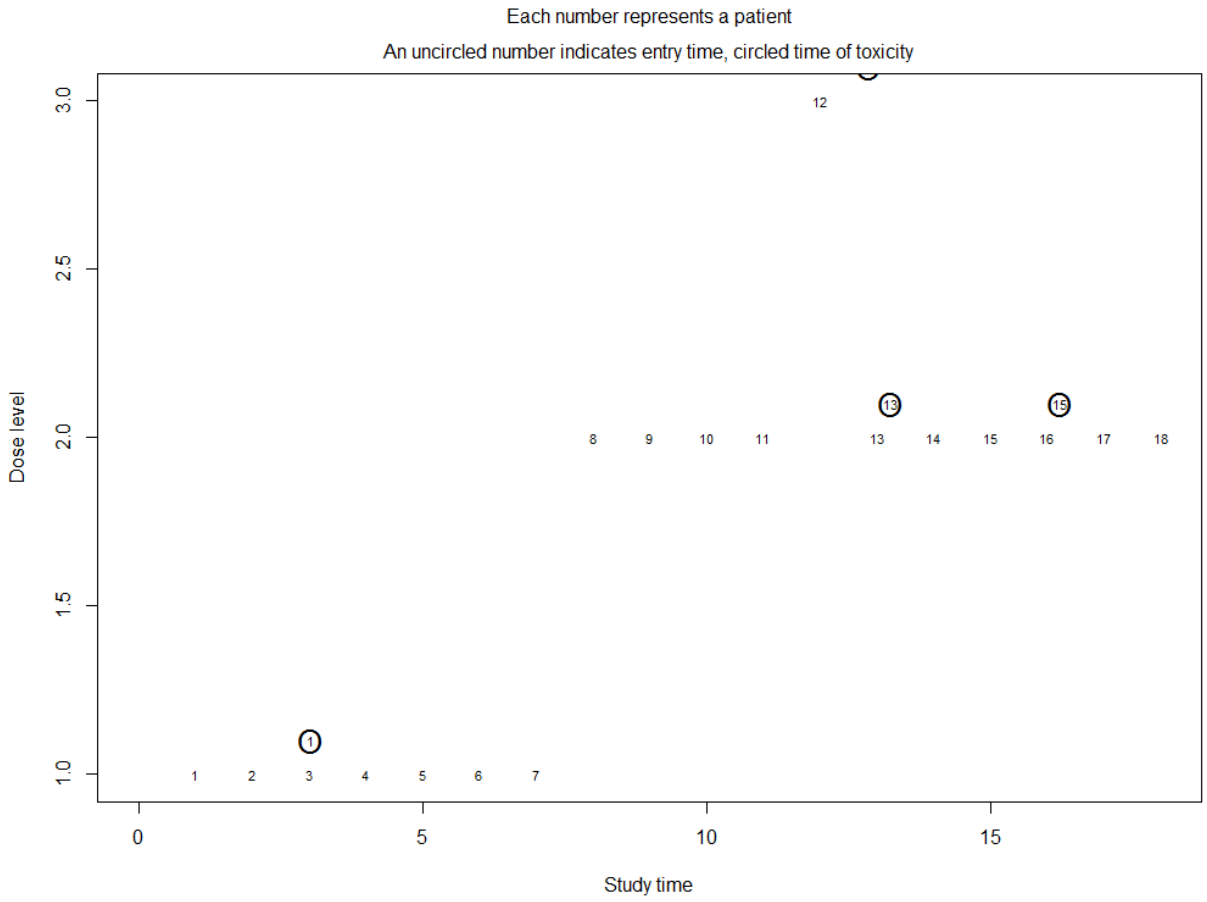

Figure 5. Simulated trial using time-to-event continuous reassessment method.
Each number represents an enrolled patient. Circled numbers depict time at which toxicity was experienced by that patient.

between 6 and 11 of the 18 patients will be assigned the MTD.

To illustrate the method using an example, Figure 5 displays a simulation of a sample design using the method based on scenario 2 (see Table 2), where the true MTD is dose level 2. In this simulated example, the recommended dose level is 2. The first three patients are assigned to dose level 1 in weeks 1, 2, and 3. By week 4 patient 1 has a DLT and we initiate the TITE-CRM with patients 4, 5, 6, and 7 being assigned dose level 1. With no DLTs, at week 7 the dose is escalated and patients 8, 9, 10 and 11 are assigned to dose level 2. With no DLTs, by week 12 the dose is escalated again and patient 12 is assigned to dose level 3. Patient 12 has a DLT and the dose is de-escalated with patient 13 to 18 being assigned to dose level 2, with two DLTs being observed among them. The estimated MTD is dose level 2 with an estimated probability of DLT of 0.27 and 90% probability interval of (0.12, 0.44). Two of the 10 patients assigned to dose level 2 have DLTs. With an accrual rate of 4 patients per month, this study takes a total of less than 6 months to complete.

4.1.1.1 Dose Limiting Toxicities for Phase 1

All patients who receive at least one dose of cobimetinib and hydroxychloroquine, with or without atezolizumab, will be evaluable for toxicity.

In order for a patient to be evaluable for DLT assessments, the patient must either incur a DLT during the DLT evaluation period, or have received at least 80% of the planned doses of hydroxychloroquine, cobimetinib, and if applicable, atezolizumab. Patients who do not fulfill one of these criteria should be considered non-evaluable for DLT assessment purposes, and be replaced.

A DLT is defined as an AE that is possibly, probably, or definitely related to study drug administration, and that is:

- Not due to the underlying malignancy;
- Has no clear evidence of an alternative etiology; and
- Meets one of the following CTCAE v.5.0 criteria during the first 28 days of hydroxychloroquine, cobimetinib, and if applicable, atezolizumab administration:
  - Any Grade ≥ 4 hematologic toxicity, except grade 4 lymphopenia, lasting ≥ 7 consecutive days
  - Grade 3 neutropenia with fever
  - Grade 3 thrombocytopenia with clinically significant bleeding
  - Any circumstance that results in dose reduction
  - Any Grade ≥ 3 non-hematologic toxicity except:
    - Nausea, vomiting, and/or diarrhea of Grade 3 severity that resolves within 7 consecutive days with optimal prophylaxis and/or treatment;
    - Grade 3 fatigue that resolves to Grade ≤ 2 within 7 consecutive days;
    - Grade ≥3 alkaline phosphatase that is related to underlying malignancy (eg, bone metastasis).
    - Grade ≥ 3 asymptomatic or mildly symptomatic rash will not be considered a DLT if the event can be adequately managed with supportive care, the event resolves to become asymptomatic and/or Grade ≤ 2 within 7 days, or the event continues for longer than 7 days in a patient who has not received appropriate supportive therapy.
    - Grade ≥ 3 elevation of serum creatine phosphokinase (CPK) level will not be considered a DLT if the event is asymptomatic (i.e., not accompanied by signs, symptoms, or other laboratory abnormalities associated with rhabdomyolysis or myocardial injury) and is deemed by the investigator to be clinically insignificant.
    - Grade 3 arthralgia will not be considered a DLT if the event can be adequately managed with supportive care or the event resolves to Grade ≤ 2 within 7 days.
    - Grade 3 fever (in the absence of any clinically significant source of fever) will not be considered a DLT if the event resolves to Grade ≤ 2 within 7 days or the event continues for longer than 7 days in a patient who has not received appropriate supportive care.

  - Grade 3 laboratory abnormality will not be considered a DLT if the event is asymptomatic and is deemed by the investigator to be clinically insignificant.
  - Grade 3 autoimmune thyroiditis or other endocrine abnormality will not be considered a DLT if the event can be managed by endocrine therapy that would not necessitate initiation of systemic corticosteroids.
- Grade ≥ 3 total bilirubin that is not attributed to disease progression
- Grade ≥ 3 AST or ALT, but not isolated elevation in ALT (non-specific) in subjects without metastatic disease in the liver
- AST or ALT ≥ 10X ULN in subjects with liver metastasis
- QTc interval ≥ 501ms confirmed by a repeat ECG
- Grade ≥ 3 Creatine Kinase with symptoms of myalgia
- Grade ≥ 2 retinal events lasting greater than 14 days or Grade ≥ 3 retinal events that are confirmed by ophthalmologic examination
- Grade ≥ 3 rash that persists despite optimal treatment, and that does not resolve to Grade ≤ 2 within 7 days.

Final decisions on determination of DLTs will be made in consultation with the Principal Investigator. The Principal Investigator may decide not to further dose escalate based on clinical judgement.

DLTs are considered AEs of special interest, and require close monitoring and rapid communication with the Principal Investigator. An DLT may be serious or nonserious. The rapid reporting of DLTs allows ongoing surveillance of these events in order to prevent enrollment of subjects at inappropriate dose levels, therefore, DLTs will be required to be reported to the study email AAAS4165@lists.cumc.columbia.edu **within 24 hours** to the lead site by memo signed by the Affiliate Site PI/Treating Investigator. DLTs should also be reported in Velos. Please refer to Section 14.2 for Data Reporting Guidelines.

4.1.1.2 Size/Accrual Rate

The planned accrual size is 18 evaluable patients, with an accrual rate of 4 patients per month.

4.1.1.3 Analysis of Primary Endpoints

The TITE-CRM will be used to estimate the probability of DLT at each dose. It will be reported along with the 90% probability interval. Moreover, the observed rate of DLT will be reported by dose level.

4.1.1.4 Analysis of Secondary and Exploratory Endpoints

The frequency of radiographic response will be documented with summary statistics at the estimated MTD and by dose level. Best overall response rate (CR+PR) will be calculated along with a 95% confidence interval.

Progression-free survival and overall survival curves will be generated using Kaplan-Meier methodology for all patients and those assigned to the estimated MTD at the end of the trial. Treatment-related toxicity will be reported by type, frequency, and severity according to the

National Cancer Institute Common Terminology Criteria for Adverse Events, version 5 (NCI, 2017).

Ten paired biopsies representing combination therapy with cobimetinib and hydroxychloroquine, with and without atezolizumab, will be performed. Once adequate tissue for exploratory analysis is procured from ten subjects, subsequent subjects may not need to undergo biopsies. Necessity will be determined by the principal investigator.

Patients will be required to obtain research-specific biopsies as follows:

- Baseline biopsy of a target lesion;
- Repeat biopsy during week 3 of Cycle 1 (for pharmacodynamic analysis);
- Optional biopsy at time of progression.

All biopsies will attempt to obtain 4-6 cores. Each core biopsy obtained from a patient will only be performed if deamed safe by the interventional radiologist. The interventional radiologist will cease from obtaining biopsies if he/she deams that additional biopsies performed from pulmonary nodules would put the patient at significant increased risk for biopsy-related complications, in which case the core biopsies should be limited to 3 cores, if feasible. Two of the cores will be processed for formalin fixation, 2 will be frozen in liquid nitrogen, and if additional core tissue is available, samples will be processed for generation of organoids and/or single cell DNA analysisfor exploratory studies.

Changes in $CD8^+$ T-cells, $FoxP3^+$ T-regs, autophagy and other markers from pre-treatment biopsies at baseline to on-treatment biopsies will be summarized and reported as means, medians, standard deviations, and ranges, and compared using the Wilcoxon signed rank test for patients assigned to the MTD. These correlative studies will be considered exploratory in nature.

Statistical analysis of RNA-Seq expression data derived from samples of the treatment arms will be carried out in the R environment for statistical computing (RDC, 2016). In order to identify differentially expressed genes between the conditions, we will make use voom-limma framework (Ritchie et al., 2015). Briefly, linear models are fit for each gene to estimate the coefficients (= effect size) and their standard error. Empirical Bayes-moderated t-statistics and their associated p-values are then used to assess the significance of the observed expression changes.

In order to evaluate concerted differences of biologically related genes, single sample gene set enrichment will be employed via the GSVA R package (Hanzelmann, Castelo, & Guinney, 2013) which produces a gene-set by sample matrix with approximately normally distributed enrichment scores which can then be compared between treatment arms using for example linear models. Detailed statistical plan is as described in the manuscript [Kenneth Olive, submitted].

4.1.2 Phase 2

The phase 2 portion of the study will be amended after preliminary safety and efficacy results from phase 1 and other ongoing clinical trials have been analyzed and a summary incorporated within the protocol as an amendment including a rationale of the cohorts to be tested. The amendment will be submitted to the Scientific Review Committee (PRMC) and Institutional Review Board (IRB) at CUIMC for approval prior to activation of phase 2 portion of the study.

Three separate phase 2 studies will be conducted based on the differences in baseline response rate by disease subtype:

Cohort 1 – Advanced Pancreas Adenocarcinoma

Cohort 2 – Advanced Colorectal Adenocarcinoma

Cohort 3 – Histology Agnostic Adenocarcinoma

The primary outcome measure is best objective response by 16 weeks; that is, patients who achieve CR or PR within the first 16 weeks will be considered responders. Tumor response will be assessed by CT scans performed every 8 weeks using the Immune-Modified Response Evaluation Criteria in Solid Tumors (IM RECIST). We will use a Simon optimal 2-stage design for each disease subtype to allow for early stopping.

Advanced Pancreas Adenocarcinoma

For the advanced pancreas adenocarcinoma group, we assume an objective response rate of 16%, based on current therapy (Wang-Gillam et al., 2016). The study will enroll 23 patients in the first stage. If 5 or more patients respond in the first stage, the study will be expanded to a total of 67 patients. If a total of 16 or more patients respond, the combination will be considered promising in patients with advanced pancreatic adenocarcinoma. This optimal two-stage design assumes for a type 1 error of 0.05 and type 2 error of 0.20 to detect a difference of 16%, versus 30% in the best objective response rate by 16 weeks.

Metastatic Colorectal Adenocarcinoma

For the advanced colorectal adenocarcinoma group, we assume an objective response rate of 2%, based on current therapy (Grothey et al., 2013; Mayer et al., 2015). The study will enroll 20 patients in the first stage. If 2 or more patients respond in the first stage, the study will be expanded to a total of 34 patients. If a total of 3 or more patients respond, the combination will be considered promising in patients with advanced colorectal adenocarcinoma. This optimal two-stage design assumes for a type 1 error of 0.05 and type 2 error of 0.20 to detect a difference of 2%, versus 15% in the best objective response rate by 16 weeks.

Advanced Histology Agnostic Adenocarcinoma

For the histology agnostic adenocarcinoma group, we assume an objective response rate of 5%, based on current therapy, and given the inclusion criteria that subjects must have progressed on or are intolerant of all standard of care therapies that result in a median progression free survival benefit of ≥ 8 weeks or an overall response rate of $> 5\%$. The study will enroll 23 patients in the first stage. If 2 or more patients respond in the first stage, the study will be expanded to a total of

56 patients. If a total of 6 or more patients respond, the combination will be considered promising in patients with histology agnostic adenocarcinoma. This optimal two-stage design assumes for a type 1 error of 0.05 and type 2 error of 0.20 to detect a difference of 5% versus 15% in the best objective response rate by 16 weeks.

4.1.2.1 Size/Accrual Rate

The planned accrual size is 157 evaluable patients across the three cohorts of patients. The expected accrual rate is 4 patients per month. However, given the possibility of early stopping, the sample size could be as low as 66 if all three cohorts stop in the first stage.

4.1.2.2 Analysis of Primary Endpoints

The frequency of best objective response (CR+PR) by 16 weeks will be calculated along with an exact 95% confidence interval.

4.1.2.3 Analysis of Secondary and Exploratory Endpoints

The frequency of radiographic response will be documented with summary statistics at the estimated MTD and by dose level. Best overall response rate (CR+PR) will be calculated along with a 95% confidence interval.

Progression-free survival (PFS) and overall survival (OS) curves will be generated using Kaplan-Meier methodology. PFS is defined as the time from enrollment until disease progression or death from any cause. Patients who are alive and have not progressed will be censored at the date of their last follow-up. OS is defined as the time from enrollment until death from any cause. Patients who are alive will be censored at their last follow-up.

4.2 Number of Patients

Phase 1: N=18

Phase 2: N=157 (66-157)

5. SUBJECT SELECTION AND WITHDRAWL

Each of the criteria in the following section must be met in order for a patient to be considered eligible for participation.

5.1 Inclusion Criteria

For *Phase 1 and 2*, participants must have histologically confirmed KRAS-mutant malignancy that is metastatic or unresectable, and for which standard curative or meaningful life prolonging palliative measures do not exist or are no longer effective as described below (#3). Subjects with pancreas adenocarcinoma or colorectal adenocarcinoma have specific requirements. **At least 12 of the 18 evaluable patients within phase 1 should carry an active diagnosis of either pancreas or colorectal adenocarcinoma.**

Specific inclusion criteria are:

1. Histological or pathological confirmation of malignancy with a KRAS-activating mutation.

Cytologic or histologic proof of malignancy needs to be verified by the treating institution pathologist, either from the initial diagnostic biopsy or from the required pre-treatment biopsy, prior to initiation of any study-related therapy. Tumor must contain an activating KRAS mutation as determined by an FDA or New York State approved non-significant risk assay (within exons 2, 3, and 4). Subjects may be enrolled using prior *KRAS* positive result by non-FDA or New York State approved assay obtained per standard of care, but may not initiate treatment until *KRAS* mutation is confirmed by an FDA or New York State approved assay. FDA approved mutational analysis tests performed on blood which identify a KRAS mutation along with a biopsy which confirms tunmor histology will be sufficient to meet this criteria.
Please note, there is specific interest in KRAS G12R mutated patients with pancreas cancer or colorectal cancer.

2. Extent of disease

Advanced disease for which no curable options are available, including but not limited to, surgery, radiation, or loco-regional therapy. Subjects who are not deemed candidates for these curative therapies will be eligible if they meet other criteria.

3. Prior treatments

- Pancreas adenocarcinoma

  Subjects must have progressed on or be intolerant of combination therapy containing either 5-Fluorouracil/Capecitabine- and/or gemcitabine-based therapy. Subjects who experienced disease recurrence while receiving adjuvant chemotherapy or within three months of completing adjuvant chemotherapy are eligible.

- Colorectal adenocarcinoma

  Subjects must have progressed on or be intolerant of combination therapy containing 5-Fluorouracil/Capecitabine, and must have received Oxaliplatin and Irinotecan.

- MSI-H/dMMR or NTRK-fusion positive tumors

  Subjects must have received prior treatment with approved drugs for tumors harboring these aberrations.

- Histology agnostic cancers other than pancreas and colorectal adenocarcinoma (see above; Phase 1 and 2)

  Subjects must have progressed on or be intolerant of all standard of care therapies that result in a median progression free survival benefit of ≥ 8 weeks, or overall response rate of >5%.

4. ECOG performance status of 0 or 1
5. Age ≥18 years
6. Adequate hematological and end-organ function (test results from within 14 days prior to initiation of study treatment):
    - ANC ≥ 1.5 x 10^9/L without granulocyte colony-stimulating factor support
    - WBC count ≥ 2.5 × 10^9/L (2500/μL)
    - Lymphocyte count ≥ 0.5 × 10^9/L (500/μL)
    - Platelet count ≥ 100 × 10^9/L (100,000/μL) without transfusion
    - Hgb > 9.0 g/dL
    - AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5X upper limit of normal (ULN), unless elevated secondary to biliary obstruction from the pancreas mass and amenable to decompression prior to initiation of therapy
    - Serum total bilirubin ≤ 1.5X ULN, unless in patients with known Gilbert disease (≤ 3X ULN), or unless elevated secondary to biliary obstruction from the pancreas mass and amenable to decompression prior to administration of investigational therapy
    - Albumin ≥ 3.0g/dL
    - Creatinine within ULN or calculated creatinine clearance (CrCl) >50 mL/min using the Cockcroft-Gault formula
    - INR and aPTT ≤ 1.5X ULN except for those who are on stable anticoagulation for at least three months.
7. Measurable disease according to IM-RECIST and tumor accessible for fresh biopsy if ten adequate paired biopsied specimens have not been procured (Phase 1)
8. Negative pregnancy test

Women of childbearing potential must have a negative serum pregnancy test at screening and must agree to use an effective form of contraception from the time of the negative pregnancy test until a minimum of 3 months after the last dose of study drug. Effective forms of contraception include abstinence, hormonal contraceptive (injectable or implantable) in conjunction with a barrier method, or a double barrier method. Women of non-child-bearing potential must have been postmenopausal for ≥ 1 year or surgically sterile.

9. Birth control agreement

Fertile men must agree to use an effective method of birth control during the study and for up to 3 months after the last dose of study drug.

10. Informed consent

Participants must be willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

11. Ability to comply

Participants must be able to comply with the study protocol, according to the investigator's judgement.

12. DVT testing

Participants must have undergone lower extremity dopplers to rule out deep venous thrombosis (DVT) within the screening period, and undergo therapeutic anticoagulation if evidence of DVT is identified.

13. VTE testing

Patients deemed at increased risk of venous thromboembolism (VTE) based on primary cancer, which includes pancreas adenocarcinoma, gastric/GE junction adenocarcinoma, or CNS malignancy, and have not been taking anticoagulants, are to undergo prophylaxis anticoagulation with enoxaparin. Enoxaparin will be administered at a dose of 1mg/kg/day to mitigate the risk of VTE. Subjects who are unable to receive enoxaparin, but deemed at increased risk of VTE will not be eligible and consultation with the Principal Investigator is required.

14. Anticoagulation treatment

Subjects who are currently stable on full-dose anticoagulation medication for at least 8 weeks are considered eligible. However, subjects who have an increased clot burden on full-dose anticoagulation, such as central pulmonary embolism, or peripheral pulmonary embolism, and DVT within the extremities will be considered eligible only with the approval of the Principal Investigator.

5.2 Exclusion Criteria

Specific exclusion criteria are:

1. Prior treatment with investigational therapy.

Participants may not have had any treatments with investigational therapy within the 28 days prior to initiation of study treatment.

2. Prior radiation therapy

Participants may not have had radiation therapy within 2 weeks prior to initiation of study treatment. Participants may not have had previous radiotherapy to 25% or more of the bone marrow.

3. Prior Therapy

Participants may not have had systemic chemotherapy within 14 days or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment.

In addition, the following prior treatment is not allowed during **Phase 1** of the study:

- Receptor tyrosine kinase inhibitors targeting MAP kinase pathway;

- Any pharmacological agents inhibiting the autophagy pathway.

In addition, the following prior treatment is not allowed during **Phase 2** of the study:

- T-cell co-stimulating agents or immune checkpoint blockade therapies, including but not limited to anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies;
- Receptor tyrosine kinase inhibitors targeting MAP kinase pathway;
- Any pharmacological agents inhibiting the autophagy pathway.

4. Adverse events from prior anti-cancer therapy

Participants may not initiate treatment if they have adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 or better, with the exception of Grade ≤ 2 peripheral neuropathy or any grade alopecia.

5. Patients currently receiving any other investigational agents
6. Concomitant treatment with other anti-neoplastic agents (hormone therapy acceptable)
7. Uncontrolled pleural effusion, pericardial effusion, or ascites
8. Patients with symptomatic brain metastases

Subjects with untreated brain metastasis ≤ 1 cm can be considered eligible if deemed asymptomatic by the investigator upon consultation with the medical monitor, and do not require immediate radiation or steroids. Subjects with brain metastasis that is treated and stable for 1 month may be considered eligible if they are asymptomatic and on stable dose of steroids, or if they do not require steroids following successful local therapy.

9. Uncontrolled hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12mg/dL, or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy.
10. Recent major surgery or significant traumatic injury

Participants may not have undergone major surgery or experienced significant traumatic injury within 14 days prior to initiating study treatment, or be recovering from a procedure related to adverse events of ≤ Grade 1.

11. Active or history of autoimmune disease or immune deficiency

Includes, but is not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

- Patients with a history of autoimmune-related hypothyroidism who are on stable thyroid-replacement hormone are eligible for the study.
- Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen

are eligible for the study.

- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
  - Rash must cover <10% of body surface area;
  - Disease is well-controlled at baseline and requires only low-potency topical corticosteroids;
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

12. History of idiopathic pulmonary fibrosis, interstitial lung disease, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan [history of radiation pneumonitis in the radiation field (fibrosis) is permitted].
13. Positive for HIV at screening or any time prior to screening

Patients without prior positive HIV test result will undergo an HIV test at screening, unless not permitted under local regulations.

14. Active Hepatitis B virus (HBV) infection (chronic or acute)

Defined as having a positive hepatitis B surface antigen (HBsAg) test at screening. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody test at screening, are eligible for the study.

15. Active hepatitis C virus (HCV) infection

Defined as positive HCV antibody test followed by a positive HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

16. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease, and inherited liver disease
17. Active tuberculosis
18. Severe infection

Patients may not have had a severe infection within 4 weeks prior to initiation of study treatment. This includes, but is not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. However, patients who were admitted for biliary tract infection due to bile duct obstruction at time of diagnosis must have a functioning biliary stent (as evidenced by declining total bilirubin and ≤ 2X ULN) and resolved infection (defined by normalization of elevated white blood cell count, absence of signs of infection) and completion of an antibiotic course (at least a seven-day course) prior to initiation of therapy.

19. Recent antibiotic treatment

Patients may not have been treated with therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment, except for biliary tract infection due to bile duct obstruction from the pancreas mass. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

20. Significant cardiovascular disease

Patient may not have significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 12 months prior to initiation of study treatment, seizure disorder, uncontrolled hypertension, or unstable arrhythmia or unstable angina within 3 months prior to initiation of study treatment.

21. Left ventricular ejection fraction below institutional lower limit of normal or below 50%, whichever is lower

22. Baseline QTcF ≥ 450 ms (males) or ≥ 470 ms (females)

23. Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment

24. Prior autologous stem cell, allogeneic stem cell, or solid organ transplantation

25. History of malignancy

Patient may not have a history of malignancy other than PDA within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year overall survival of > 90%), such as adequately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma *in situ*, or Stage I uterine cancer.

26. Recent vaccination

Patients may not have been treated with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipate the need for such a vaccine during treatment with atezolizumab or within 5 months after the last dose of atezolizumab.

27. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins

28. Known allergy or hypersensitivity to 4-aminoquinoline compounds or any of the study drug excipients

29. Recent immunosuppressive treatment

Patients may not have been treated with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor alpha agents) within 2 weeks prior to initiation of study treatment, or

anticipate the need for systemic immunosuppressive medication during the course of the study, with the following exceptions:

- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study if receiving equivalent to < 10mg of prednisone daily.
- Patients who received a one-time pulse dose of systemic immunosuppressant medication are eligible for the study after approval from the Principal Investigator.

30. Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications

31. History of retinal pathology

Patients may not have a history of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment, central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration. Specifically, patients will be excluded from study participation if they currently are known to have any risk factors for RVO, including:

- Glaucoma with intraocular pressure ≥ 21 mmHg;
- Grade ≥ 2 serum cholesterol;
- Grade ≥ 2 hypertriglyceridemia;
- Grade ≥ 2 uncontrolled hypertension (patients with a history of hypertension controlled with anti-hypertensive medication to Grade ≤ 1 are eligible).

32. Pregnancy

Pregnant women are excluded from this study because there is an unknown, but potential risk for AEs in nursing infants secondary to treatment of the mother with these agents; breastfeeding should be discontinued.

33. Other contraindicated conditions

Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications in the opinion of the treating investigator.

34. Concomitant strong CYP3A4 inhibitors and inducers

Refer to list of common CYP3A4 inhibitors and inducers (Appendix 2). These include anticonvulsants, mycin antimicrobials, and antiretrovirals. Some common examples include inhibitors, such as erythromycin, fluoxetine, gemfibrozil, and inducers, such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine. Concomitant treatment is permitted if the

medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration.

35. Uncontrolled psoriasis, porphyria, proximal myopathy or neuropathy
36. Severe depression

Subjects hospitalized for depression within the past 2 years, or who have prior suicidal attempts will be excluded.

37. Gluocose-6-phosphate dehydrogenase (G-6-PD) deficiency
38. History of connective tissue disorders (e.g., lupus, scleroderma, arteritis nodosa)
39. Subjects on greater than once daily dose of antacid therapy
40. Concomitant use of any of the following drugs:
    - Digoxin
    - Pharmacological agents known to prolong QT interval
    - Mefloquine or other agents which may lower the convulsive threshold
    - Antiepileptics
    - Methotrexate
    - Cyclosporine
    - Ampicillin
    - Cimetidine

5.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. See Table 3 below for specific accrual targets.

Table 3. Accrual Targets

Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	5	+	9	=	14
TOTAL	**7**	**+**	**11**	**=**	**18**
Racial Category					

American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	1	+	1	=	2
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	6	+	10	=	16
TOTAL	7	+	11	=	18
	(A1 = A2)		(B1 = B2)		(C1 = C2)

5.4 Subject Recruitment

Patients will be recruited for the study from investigator or co-investigator clinical practices and referring physicians.

5.5 Early Withdrawal of Subjects

5.5.1 When and How to Withdraw Subjects

- If at any time the patient develops progressive disease, he/she will be taken off treatment and referred for alternative therapy.
- If at any time the patient develops unacceptable toxicity, he/she will be removed from study treatment.
- If at any time the patient is found to not meet key eligibility Criteria for Patient/Subject Eligibility (e.g., a change in diagnosis), the patient will be removed from study.
- If the patient fails to comply with the defined treatment plan and follow-up evaluations, the patient will be removed from the study treatment.
- If the patient withdraws consent for continued participation, he/she will be removed from study treatment. Patient may agree to be contacted for follow up data.

5.5.2 Data Collection and Follow-up for Withdrawn Subjects

If a patient withdraws consent to participate in the study treatment administration, every attempt will be made to follow up for survival data.

6. REGISTRATION PROCEDURES

6.1 CUIMC Research Participant Registration

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same-day subject registrations (and after hour registrations) will be accommodated on a case-by-case basis, provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

The following requirements exist for participant registration:

- Confirm eligibility, as defined in the section entitled Criteria for Subject Eligibility.
- Obtain informed consent by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.
- Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB-approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.305.5292, with the subject line "AAAS4165 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- Completed/signed study-specific Eligibility Checklist (signed by Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
  - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
  - Copy of pathology and surgical reports
  - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

Subject line of email or fax should read: "AAAS4165 Complete Subject Registration Request (PHI)".

Upon receipt of documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, email queries to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team to include eligibility/enrollment status and subject ID information. Protocol therapy may not be initiated prior to receipt of this notification.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7. TREATMENT AND/OR IMAGING PLAN

7.1 Investigational Agent Administration

Treatment will be on an outpatient basis. Reported AEs and potential risks for cobimetinib, hydroxychloroquine, and atezolizumab are described below (Section 8, Appendix 1). Appropriate dose modifications are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered to treat the patient's malignancy.

Patients will receive treatment as outlined in Table 4 below until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic

and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 4. Treatment schedule

Cycle	Cycle Length	Dose, Route and Regimen (drugs listed in order of administration)
Cycle 1 and beyond	28 days	• Cobimetinib[a] orally once daily (morning) on Days 1-21 of each 28-day • Hydroxychloroquine: 600mg orally twice daily on Days 1-28 of each 28-day cycle • Atezolizumab None or 840 mg IV on Days 1 and 15 of each cycle

[a]Dose will be determined via dose levels

If one study drug is discontinued, the other study drug(s) can be continued if the patient is likely to derive clinical benefit, as determined by the investigator in consultation with the Principal Investigator.

7.1.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle (Section 7.3).

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Atezolizumab administration will be according to Table 5 below. Please note that Hydroxychloroquine and Cobimetinib could be administered in the morning, prior to Atezo.

Table 5. Atezolizumab administration

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion and 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion, or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

Atezolizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures) with Principal Investigator approval. The Investigator and Principal Investigator will determine the acceptable length of treatment interruption.

7.1.1.1 Premedication

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. Hematopoietic growth factors are not to be administered prophylactically prior to the first dose of therapy. In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard 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 ß2-adrenergic agonists; see Appendix 1.

7.1.2 Cobimetinib

In this study, cobimetinib will be administered orally once daily (morning) on Days 1-21 of each 28-day cycle. Cobimetinib will be supplied as 20-mg, film-coated tablets packaged in blister packs (21 tablets per pack; 3 packs per box) for oral administration. Cobimetinib should be taken approximately the same time in the morning, and no later than 4 hours after the scheduled time. Cobimetinib may be taken with or without a meal. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. For information on the formulation and handling of cobimetinib, see the pharmacy manual and the Cobimetinib Investigator's Brochure.

7.1.3 Hydroxychloroquine

In this study, Hydroxychloroquine will be administered orally twice daily on Days 1-28 of each 28-day cycle with a meal or a glass of milk. Hydroxychloroquine should be swallowed whole with a glass of water (with meals) or milk and should not be chewed, cut, or crushed. If a dose of Hydroxychloroquine is missed (i.e., not taken within 6 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Hydroxychloroquine treatment may be suspended for reasons other than toxicity with Principal Investigator approval.

7.1.4 Other Agent(s)

N/A

7.1.5 Other Modality(ies) or Procedures

N/A

7.2 General Concomitant Medication and Supportive Care Guidelines

The following are permitted therapies while receiving investigational agents.

- Oral contraceptives
- Hormone-replacement therapy
- Been stable on anticoagulation therapy (at a stable dose or low-molecular-weight heparin) that was initiated at least two months prior to initiation of study treatment.
- Inactivated influenza vaccinations
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical

insufficiency amounting to less than 10mg of prednisone daily, and with the approval of the Principal Investigator.

- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Nerve blocks for pain control with adequate pain management

7.2.1 Medications to be given with precaution due to effects related to cytochrome P450 enzymes

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration.

Concomitant use of strong and **moderate inhibitors of CYP3A** (e.g., clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole; see Appendix 2) should be avoided during cobimetinib treatment because cobimetinib is a sensitive substrate of CYP3A, and exposures will be increased in the presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects). Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of study treatment.

Strong and **moderate CYP3A inducers** (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital; see Appendix 2) should be avoided during cobimetinib treatment because they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

The above lists of cautionary medications are not necessarily comprehensive. The Investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the Investigator should contact the Principal Investigator if questions not listed above arise regarding medications.

7.2.2 Medications Prohibited

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited within 12 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide,

azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.

7.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 1 cycle or until one of the following criteria applies:

- Confirmed disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator

7.4 Duration of Follow Up

Participants will be followed for up to 5 years after completion or removal from study treatment or until death, whichever occurs first. Participants removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. A post-study follow-up contact via phone by site staff will be conducted every 3 months during years 1 and 2, then every 6 months thereafter to obtain information on any new anti-cancer therapy received and survival status.

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

• The site will attempt to contact the participant and reschedule the missed visit within 2 weeks, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.

• Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, at least 3 telephone attempts). These contact attempts should be documented in the participant’s medical record or study file.

• Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.5 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 7.4 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

8. ADVERSE EVENTS AND DOSING DELAYS/MODIFICATIONS

8.1 General guidelines on dose delays and/or modifications

Dose Modifications –

Dose reductions during the DLT period are not allowed, unless a DLT is confirmed. If the subject experiences a DLT, they should be removed from the study unless the subject is deriving clinical benefit, as determined by the Investigator in consultation with the Principal Investigator.

Dose modifications will be allowed if subject does not tolerate therapy after the DLT period, as described (Section 8.2).

Dose Interruptions –

Dose interruptions are allowed during the DLT period as long subjects receive 90% of the scheduled doses. Doses held due to toxicity will not be replaced within the same cycle. If a drug is held due to toxicity, the other drug(s) may be administered as scheduled. If hydroxychloroquine and/or cobimetinib is held for longer than 28 days, all treatments should be permanently discontinued and the patient removed from study, unless the subject is deriving clinical benefit as determined by the Investigator in consultation with the Principal Investigator. If atezolizumab is held for longer than 105 days, atezolizumab should be permanently discontinued; however, hydroxychloroquine and cobimetinib may be continued.

8.2 Drug-specific dose delays/modifications

8.2.1 Dose modifications: Atezolizumab

There will be no dose modifications for atezolizumab in this study. Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >105 days, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >105 days to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >105 days if the Principal Investigator agrees that the patient is likely to derive clinical benefit. Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology. Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the

immune related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both, the Investigator (or an appropriate delegate) and the Principal Investigator. Please refer to Appendix 1 for management of atezolizumab-related adverse events.

8.2.2 Dose modifications: Cobimetinib

Allowable dose modifications for Cobimetinib are described in Table 6. Cobimetinib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. After dose reduction, the dose of cobimetinib may be escalated by a maximum of one dose level (20 mg) increments at the Investigator's discretion in consultation with the Principal Investigator, provided there are no safety concerns. If cobimetinib has been withheld for >28 days because of toxicity, the patient should be discontinued from cobimetinib, unless resumption of treatment is approved following Investigator discussion with the Principal Investigator. The Principal Investigator should be consulted for any major surgery (e.g., involving a body cavity), and cobimetinib should generally be withheld for 12 hours prior to the procedure and for 2 weeks thereafter.

Table 6. Cobimetinib dose modifications

Dose Level	Cobimetinib (mg) TDD
-1	40mg (orally in AM)
-2	20mg (orally in AM)

8.2.3 Dose modifications: Hydroxychloroquine

Allowable dose modifications for Hydroxychloroquine are described in Table 7.

The 4-aminoquinoline compounds are very rapidly and completely absorbed after ingestion. In accidental overdosage, or rarely with lower doses in hypersensitive patients, toxic symptoms may occur within 30 minutes. The symptoms of overdosage may include headache, drowsiness, visual disturbances, cardiovascular collapse, convulsions, hypokalemia, rhythm and conduction disorders, including QT prolongation, torsades de pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden, potentially fatal respiratory and cardiac arrest. Treatment is symptomatic and must be prompt. Immediate gastric lavage until the stomach is completely emptied is indicated. After lavage, activated charcoal is introduced by the stomach tube within 30 minutes of ingestion of the drug may inhibit further intestinal absorption. To be effective, the dose of activated charcoal should be at least five times the estimated dose of hydroxychloroquine ingested.

Consideration should be given to administering diazepam parenterally since studies suggest that it may be beneficial in reversing chloroquine and hydroxychloroquine cardiotoxicity.

Respiratory support and shock management should be instituted as necessary.

Exchange transfusions are used to reduce the level of 4-aminoquinoline drug in the blood.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least six hours. Fluids may be forced and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine. This will promote urinary excretion in cases of both overdosage and sensitivity. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

Table 7. Hydroxychloroquine dose modification

Dose Level	Hydroxychloroquine (mg) TDD
-1	1000mg (400mg AM and 600mg PM orally)
-2	800mg (400mg BID orally)
-3	600mg (200mg AM and 400mg PM orally)

8.2.4 Dose modifications: Cobimetinib + Hydroxychloroquine with or without Atezolizumab therapy

Dose modification may be made for Cobimetinib and/or Hydroxychloroquine, as necessary, according to the guidelines described (Table 6 and 7), as guided in Appendix 1. If further dose reduction of cobimetinib is indicated after two dose reductions, the patient must discontinue cobimetinib. Similarly, if further dose reduction of hydroxychloroquine is indicated after three dose reductions, the patient must discontinue hydroxychloroquine. Subjects may continue treatment if being administered two of the three study drugs, but may not continue on study with either cobimetinib, hydroxychloroquine, or atezolizumab alone, unless with the approval of the Principal Investigator deeming the subject to be deriving clinical benefit.

8.3 Management of adverse events

The following categories of adverse events have been associated with one or more of the study drugs:

- Infusion related reactions (IRRs), anaphylaxis, and hypersensitivity reactions
- Gastrointestinal toxicity
- Dermatologic toxicity
- Hepatic toxicity
- Pulmonary events
- Endocrine disorders
- Pancreatic events

- Neurologic disorders
- Ocular toxicity
- Cardiotoxicity
- Hemorrhage
- Myositis

Specific actions to be taken in each case as described in Appendix 1.

Adverse events of special interest must be reported by the investigator to the Principal Investigator immediately (i.e., no more than 24 hours after learning of the event; see Section 9.5 for reporting instructions). Adverse events of special interest for this study include the following:

Non-Drug Specific Adverse Events of Special Interest:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study treatment. 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 Specific Adverse Events of Special Interest

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, or hyperthyroidism and hypophysitis
- Hepatitis, or AST or ALT >10 x ULN
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenia gravis or myasthenic syndrome, meningoencephalitis

- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness and systemic inflammatory response syndrome.
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Cobimetinib Specific Adverse Events of Special Interest

- Any grade Retinal vein occlusion
- Any grade serous retinopathy including retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Rhabdomyolysis or Grade ≥3 CPK elevation
- Grade ≥3 hemorrhage or any grade cerebral hemorrhage
- Grade ≥3 rash
- Grade ≥3 diarrhea
- Symptomatic heart failure or Grade ≥ 2 left ventricular dysfunction
- Pneumonitis
- AST and/or ALT > 10 X ULN

8.3.1 Cobimetinib-associated adverse events

For specific guidelines on how to respond to adverse events associated with cobimetinib, see Appendix 1.

The following adverse events are classified as identified risks associated with cobimetinib: serious retinopathy, left ventricular dysfunction, severe hemorrhage, rhabdomyolysis, and pneumonitis. The following adverse events are classified as potential risks for cobimetinib: severe hepatotoxicity (Grade ≥3), impaired female fertility, and teratogenicity and developmental toxicity. In addition, there is the possibility of drug-drug interactions in patients treated with cobimetinib. Clinical and safety data were reported that included monotherapy and combination

studies, of which key adverse events are summarized here, but for a complete review of the safety data please refer to the most current IB version.

Common (>10%) adverse events observed with Cobimetinib included bleeding, serious retinopathy, diarrhea, nausea, emesis, rash, pyrexia, chills, anemia, increased liver function enzymes, increased creatinine phosphokinase, and photosensitivity. Less common (1% - 10%) adverse events included decreased left ventricular ejection, risk of basal and squamous cell carcinoma, kertocanthoma, dehydration, hyponatremia, hypophosphatemia, hyperglycemia, and pneumonitis. Guidelines for treatment interruption or discontinuation in the case of adverse events are described in Appendix 1.

Cobimetinib should be permanently discontinued for:

- Grade 4 hemorrhage events attributed to cobimetinib
- Symptomatic or asymptomatic decrease of LVEF < 40% or ⩾ 10% absolute decrease from baseline after treatment break or recurrent symptomatic absolute decrease of LVEF < 10% (See Table 1 for details)
- Rhabdomyolysis or symptomatic CPK elevations not improving within 4 weeks of dose interruption
- Liver laboratory abnormalities not resolving to Grade ⩽1 within 4 weeks of dose interruption or if Grade 4 liver laboratory abnormalities recur after initial improvement
- QTc increase meets values of both > 500 ms and > 60 ms change from pre-treatment values or 3rd occurrence of QTc > 500 ms during treatment and change from pre-treatment value remains ⩽ 60ms

9. ADVERSE EVENTS: REPORTING REQUIREMENTS

9.1 Definitions

9.1.1 Adverse Event:

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human patient, including abnormal sign, symptom or disease, temporally associated with the patient's participation in research, whether or not considered related to the patient's participation in the research. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- Results in study withdrawal;
- Is associated with a serious adverse event;
- Is associated with clinical signs or symptoms;
- Leads to additional treatment or to further diagnostic tests;

- Is considered by the investigator to be of clinical significance, including:
  - AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with pancreatic adenocarcinoma that were not present prior to the AE reporting period;
  - Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures, such as cardiac catheterizations);
  - If applicable, AEs that occur prior to assignment of study treatment that are associated with medication washout, no treatment run-in, or other protocol-mandated intervention;
  - Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Please note: This study will utilize Common Terminology Criteria for Adverse Events **(CTCAE) v.5** (NCI, 2017) for all AE reporting criteria. (See Section 9.2 for adverse event severity grading scale for events not specifically listed in NCI CTCAE)

The maximum severity grade of AEs or the worsening of a pre-existing medical condition occurring during the study should be recorded, regardless of relationship to study medication.

For the purposes of this study, progression of the subject's underlying disease ("disease progression") is an efficacy assessment and should not be reported as an AE or SAE. However, if the investigator determines that there is evidence suggesting a causal relationship between the event and the study medication, the event should be reported immediately to the safety contact and recorded as an AE or SAE.

9.1.2 Serious Adverse Event (SAE):

AEs are classified as serious or non-serious. A serious adverse event is any AE that is:

- Fatal;
- Life-threatening;
- Requires inpatient hospitalization/prolongation of existing hospitalization, unless:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control);
  - Elective or pre-planned treatment for a preexisting condition that is unrelated to the indication under study;
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital admission;

  - Social reasons and respite care in the absence of any deterioration in the patient's general condition;

- Results in persistent or significant disability or incapacity;
- A congenital anomaly or birth defect;
- An important medical event (i.e., those that may not be immediately life threatening, but are clearly of major clinical significance. For example, drug overdose or abuse, seizure that does not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department).

Any AE that does not meet any of the above criteria should be regarded as non-serious adverse events.

9.1.3 Unanticipated Problem:

An unanticipated problem (UP) is any incident, experience, or outcome involving risks to patients or others in any human patient/patient research that meets <u>all</u> of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given: (a) the research procedures that are described in the IRB-approved protocol and informed consent document, and (b) the characteristics of the patient population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.2 Assessment

At each contact with the subject, the investigator must seek information on AEs through specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source document, and also in the appropriate AE module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document; they should be grouped under one diagnosis.

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

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

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study

treatment or participation is not the cause. Serious AEs that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), study collaborators, and Genentech, Inc., in accordance with CFR 312.32 [Investigational New Drug (IND) Safety Reports].

Safety assessments will consist of monitoring and reporting AEs and SAEs, per protocol. This includes all events of death, and any study specific issue of concern. The AE severity grading scale for the NCI CTCAE (v. 5) will be used for assessing AE severity. To assess severity of AEs that are not specifically listed in the NCI CTCAE, see Table 8.

Table 8. Adverse event severity scale for events not listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE 5.0, which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

9.3 Relationship to Study Intervention

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and

end dates), regulatory seriousness criteria if applicable, suspected relationship to atezolizumab and/or cobimetinib (see following guidance), and actions taken.

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

Yes

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

No

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

Expectedness

Expected adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Identify the source of the reference safety information used to determine the expectedness of the AE (e.g., IB, approved labeling). Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study intervention.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or device labeling, or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, or is not consistent with the risk information described in the protocol, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB or package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB or package insert listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the study intervention, but are not specifically mentioned as occurring with the particular study intervention under investigation.

The Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.4 Recording and Reporting Adverse Events

9.4.1 Specific Instructions for Recording Adverse Events

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

9.4.1.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.4.1.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 9.4.7.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

9.4.1.3 Preexisting Medical Conditions

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

9.4.1.4 Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

- Diagnostic or elective surgical procedures for preexisting conditions;
- Efficacy measurement for the study; or
- Scheduled therapy of the target disease of the study.

9.4.1.5 Pregnancy

If a female patient becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, a report should be completed and expeditiously submitted to Columbia University who will report on behalf of all sites to its collaborators, Genentech, Inc., and Halozyme.. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to the cobimetinib, atezolizumab and/or Hydroxychloroquine should be reported as an SAE.

9.4.1.6 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior exposure to cobimetinib, atezolizumab and/or Hydroxychloroquine . If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

For studies involving collection of survival data and follow up until progression-free period, the investigator, after the end of the AE reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any SAE, including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject, including pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drug

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single Case Reports.

9.4.1.7 Abnormal Laboratory Values

All abnormal laboratory values that are gradable per National Cancer Institute (NCI) CTCAE criteria; will be documented as toxicities regardless of grade, attribution, or clinical significance. They must be documented in the medical record directly, to include the CTCAE grade and applicable attribution pertaining to the investigational products. If the laboratory abnormality suggests a disease and/or organ toxicity and/or requires active management, the suspected cause and course of management should also be documented.

9.4.2 Adverse Events of Special Interest to be Reported Immediately to the Collaborator: Genentech

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

Affiliate sites should report directly to CUMC, who will report to Genentech on behalf of Affiliate sites.

See section 8.3 for **AEs which are considered of special interest and must be reported to the Principal-Investigator by the affiliated sites within 24 hours of the awareness date** and must be reported to the Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria within 15 calendar days of awareness date. (See section 9.4.5 for AESI reporting timeline)

9.4.3 Case Transmission Verification of Single Case Reports and Exchange of single case reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via *Sponsor Investigator* emailing Genentech a Quarterly line-listing documenting single case reports sent by *Sponsor Investigator* to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by *Sponsor Investigator* to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

Investigator will track all protocol-defined AE, AESI, Product Complaints (with or without an AE) and Special Situation Reports (including pregnancy reports) originating from the Study for atezolizumab and cobimetinib. Investigators must report all SAEs, protocol-defined AE, AESI, Product Complaints (with or without an AE) and Special Situation Reports (including pregnancy reports) to Columbia University within the timelines described below, using the HICCC DSMC SAE Report Form. The completed SAE report form should be sent immediately upon completion to Columbia University. Affiliate sites should report directly to CUMC, who will report simultaneously to Genentech Drug Safety at:
(**fax**) 650-238-6067 or (**email**) usds_aereporting-d@gene.com.

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

Email: kaiseraugst.global_impcomplaint_management@roche.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request by Genentech

9.4.4 Reporting to Genentech

Adverse events, serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), Product Complaints (with or without an AE) and other Special Situation Reports where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be sent either electronically or by fax and within the timelines specified below:

- **Serious Adverse Drug Reactions (SADRs)**

Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Pregnancy reports**

While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

- **AESI reporting to Genentech**

AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **Product Complaints**

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Special situation reports

In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, off-label use, misuse, or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population).

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.

It is understood and agreed that the Sponsor will perform adequate due diligence with regard to obtaining follow-up information on incomplete AE, Special Situations and pregnancy reports.

9.4.5 Reporting of Serious Adverse Events

9.4.5.1 Adverse Event Reporting Period

The recording of AEs will begin at the start of the administration of the first dose of a study medication, with the exception of study-procedure-associated SAEs. Any AE that occurs after the time of ICF signature will be recorded as an SAE if the event is associated with a study procedure and meets criteria of seriousness, even if the subject has not yet received any study medication. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment, or 30 days **following the decision to remove the patient from study treatment, whichever is earliest for all non-serious and serious adverse events.** After this period, investigators will follow subjects for SAEs and AESI activity up to 90 days from last does of atezolizumab. After that period of time, investigators should only report SAEs that are attributed to prior study treatment.

9.4.5.2 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

9.4.5.3 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is

serious, unexpected, and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Sponsor-Investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations

The Sponsor-Investigator will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of cobimetinib and hydroxychloroquine either alone or with atezolizumab. An unexpected adverse event is one that is not already described in cobimetinib, hydroxychloroquine and atezolizumab's Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug, must be reported as soon as possible, but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting.
- The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of cobimetinib and hydroxychloroquine either alone or with atezolizumab. An unexpected adverse event is one that is not already described in cobimetinib, hydroxychloroquine or atezolizumab's investigator brochure.
- Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.
- Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event.

- Any findings from animal or *in vitro* testing, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible, but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting.
- Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or Investigator Brochure.
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

9.4.5.4 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting must occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

All SAEs must be reported using the HICCC DSMC Serious Adverse Event Reporting Form and submitted to the central HICCC DSMC email at: HICCC_DSMC@lists.cumc.columbia.edu.

Any events that qualify for FDA reporting to the applicable IND/IDE, must be vetted through the CPDM IND officer, in collaboration with the applicable regulatory staff.

All serious adverse events (SAEs) will be followed until satisfactory resolution, or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the HICCC DSMC and should be provided as soon as possible.

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

9.4.5.5 Reporting to Drug Manufacturer by Sponsor-Investigator

Investigators must report all SAEs to Columbia University/Sponsor/Investigator within the timelines described below, using the HICCC DSMC SAE Report Form. The completed SAE report form should be sent immediately upon completion to Columbia University. Affiliate sites should

report directly to CUMC, who will report simultaneously to Genentech Drug Safety at: (**fax**) 650-238-6067 or (**email**) usds_aereporting-d@gene.com.

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request. SAEs, pregnancy reports and adverse events of special interest (AESIs), where the patient has been exposed to the Product, will be sent on a DSMC SAE Report Form or equivalent to the Roche contact. Transmission of these reports (initial and follow-up) will be sent either electronically or by fax and within the timelines specified above for both Genentech.

Sponsor-Investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study.

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

Genentech

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

STUDY CLOSE-OUT

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

imCORE-USMA-OPS-d@gene.com
And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by *Sponsor-Investigator*. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. *Sponsor-Investigator* agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. *Sponsor-Investigator* agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

10. PHARMACEUTICAL INFORMATION

10.1 Atezolizumab, Cobimetinib, and Hydroxychloroquine

10.1.1 Description

Atezolizumab

Atezolizumab is a monoclonal antibody which binds to PD-L1. The antibody lacks the N-linked oligosaccharides due to an asparagine to alanine substitution at position 298 of each heavy chain resulting in a non-glycosylated antibody.

Injection for intravenous use is a sterile, preservative-free, colorless-to-slightly-yellow solution in single-dose vials. Each mL of TECENTRIQ contains 60 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg), polysorbate 20 (8 mg), pH 5.8.

Cobimetinib

Cobimetinib is a small molecule inhibitor of MEK that is being developed as an anti-cancer therapeutic intended for oral administration. Cobimetinib is approved in multiple countries including United States, European Union, Switzerland, and across the world for use with vemurafenib for the treatment of advanced BRAF-mutated melanoma. Cobimetinib Drug Product is supplied as a 20 mg film coated, immediate-release tablet. Furthermore, a powder for oral suspension, 250 mg formulation (corresponding to a cobimetinib concentration of 4.8 mg/ml after reconstitution), filled in multi-dose containers is provided for pediatric patients and adults facing difficulties in swallowing tablets.

Food-effect studies demonstrated that cobimetinib pharmacokinetics were not altered in the fed state when compared to the fasted state. High-fat meal or proton pump inhibitors did not affect cobimetinib pharmacokinetics. CYP3A4 inhibitors, such as itraconazole, significantly altered cobimetinib elimination with an approximately 7-fold increase in cobimetinib maximum concentration. Additionally, because cobimetinib is a sensitive substrate of CYP3A, it is likely that

cobimetinib exposures will be significantly lower in the presence of CYP3A inducers. Patients with severe hepatic impairment led to a reduction in total cobimetinib exposure, which is not considered to be clinically significant.

Hydroxychloroquine

Hydroxychloroquine is a small water soluble compound (MW 433.95) that is dispensed in 200 mg tablets for oral administration. In healthy males, peak blood concentration was reached in 3.26 hours with a half life of 537 hours (22.4 days). The plasma peak concentration was reached in 3.74 hours with a half life of 2,963 hours (123.5 days). The long half-life can be attributed to extensive tissue uptake rather than through decreased excretion. In subjects taking the drug chronically for six months, renal clearance of the drug appeared similar.

Hydroxychloroquine is prescribed for Malaria, Rheumatoid Arthritis, and Systemic Lupus Erythematosus by an unknown mechanism.

10.1.2 Treatment Regimen

Atezolizumab

Atezolizumab 840 mg over 60 mins (± 15 mins) IV on days 1 and 15 every 28 day cycle.

Cobimetinib

To be taken by mouth once daily with or without meal at the recommended daily dose on days 1 through 21 every 28 days.

Patients will receive cobimetinib at the recommended daily dose orally once daily (20 mg tablets) in the morning on Days 1-21 of each 28-day cycle. Cobimetinib should be taken approximately the same time each day, and no later than 4 hours after the scheduled time. Cobimetinib may be taken with or without a meal. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Hydroxychloroquine

Hydroxychloroquine should be taken by mouth twice daily (200 mg tablets) with meals or with a glass of milk at the recommended daily dose. Hydroxychloroquine should be taken approximately at the same time each day, and no later than 4 hours after the scheduled time. Hydroxychloroquine should be swallowed whole with a glass of water (with meals) or milk and should not be chewed, cut, or crushed. If a dose of Hydroxychloroquine is missed (i.e., not taken within 6 hours after

the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

10.1.3 Method for Assigning Subjects to Treatment Groups

Phase 1 – Hybrid 3+3 and TITE CRM (see Section 4.1)

10.1.4 Preparation and Administration of Study Drug

Atezolizumab

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be stored per the manufacturer's label upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

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

The dose level of atezolizumab to be tested in this study is 840 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 2 weeks for two doses pre-surgery and 4 doses post-surgery. Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (+/- 15) minutes (see Table 5). If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (+/- 10) minutes. If the 30 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (+/- 10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, 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. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Describe in detail all the steps necessary to properly prepare the investigational agent. Include whether the drug preparation will be done in a pharmacy or by a study team member. Fully describe how the study treatment is to be administered. If study drug is stored, mixed/prepared or dispensed from the CUMC Research Pharmacy, that should be noted here, including the contact number to that service office.

Cobimetinib

Dispense in a tight, light-resistant container as defined in the USP/NF. Keep out of the reach of children. Store at room temperature [20° to 25°C (68° to 77°F), allows excursions between 15° and 30°C (59° and 86°F)].

Hydroxychloroquine

Dispense in a tight, light-resistant container as defined in the USP/NF. Keep out of the reach of children. Store at room temperature [20° to 25°C (68° to 77°F), allows excursions between 15° and 30°C (59° and 86°F)].

10.1.5 Subject Compliance Monitoring

Oral study drugs (if applicable) will be provided only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Any discrepancy regarding the dose administered, and the reason for the discrepancy, will be recorded in the eCRF. At each clinic visit, patients will be questioned about their compliance with study drug administration, and their dosing diary should be reviewed.

10.1.6 Prior and Concomitant Therapy

Refer to Inclusion/Exclusion criteria (Sections 5.1 - 5.2).

10.1.7 Packaging

Please refer to the package insert or the most current version of the Investigator Brochure for details.

10.1.8 Blinding of Study Drug

N/A

10.1.9 Receiving, Storage, Dispensing and Return

10.1.9.1 Receiving

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the

designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify agent manufacturer of any damaged or unusable study treatments that were supplied to the investigator's site.

10.1.9.2 Storage

Please refer to the package insert or the most current version of the Investigator Brochure for details.

10.1.9.3 Dispensing of Study Drug

The Study drug provided in accordance with this Protocol will be kept in a secure place, and will only be supplied to patients participating in this Study. The PI is accountable for all Study drug supplied by Genentech in accordance with this Protocol. In addition, the PI must keep accurate and up-to-date dispensation records. Any Study drug accidently or deliberately destroyed must be recorded in a timely fashion, including an explanation for the destruction in writing. Any discrepancies between the amounts of Study drug dispensed and returned must also be explained in writing. All such records of drug accountability must be entered on the corresponding Patient CRF's.

10.1.9.4 Destruction of Study Drug

All unused and partially used Study drug must be sealed and returned to the PI or his/her designee, or destroyed on Site in accordance with the established procedures for drug destruction, and with approval by the PI or his/her designee. Details of destruction, including, but not limited to, the number of boxes destroyed, batch number, and the date and method of destruction must be recorded on the Study drug destruction logs.

11. STUDY CALENDAR

The schedule of assessments is detailed in Table 10 below.

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans must be done ≤ 2 weeks prior to the start of therapy. 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.

Unless otherwise noted below, all assessments (e.g., labs, imaging, physical exam, vitals, etc.) will follow the CPDM departmental SOP "Guidelines for Timing of Protocol Required Procedures". Any activities that would fall within those pre-determined windows will not be considered deviations/violations of protocol procedures.

11.1 Pharmacokinetics Assessments

On days with PK assessments, patients ***should not*** eat breakfast ***or*** take cobimetinib or hydroxychloroquine at home. Upon arrival to the clinic after undergoing pre-dose PK draw, they will take medications with a glass of milk and eat breakfast, as instructed by clinic staff.

Table 9. PK Assessments

Treatment Cycle	Day	PK Sample # Hydroxychloroquine (HCQ) [a] (Whole Blood)	PK Sample # Cobimetinib (Cobi) [a] (Plasma)	Time Relative to Dose
1	1	101	201	Pre-dose[b]
1	1	102	202	1hr ± 5 min
1	1	103	203	2hr ± 5 min
1	1	104	204	4hr ± 5 min
1	8	105	205	Pre-dose[b]
1	8	106	206	1hr ± 5 min
1	8	107	207	4hr ± 5 min
1	15	108	208	Pre-dose
1	15	109	209	1hr ± 5 min
1	15	110	210	4hr ± 5 min
2	1	111	211	Pre-dose
2	1	112	212	1hr ± 5 min
2	1	113	213	4hr ± 5 min
N/A	N/A	5101+	5201+	Anytime[c]

[a] Hydroxychloroquine (HCQ) will be measured in whole blood and Cobimetinib will be measured in plasma

[b] Pre-dose levels should be drawn just prior to administration of Cobimetinib (Cobi) and Hydroxychloroquine (HCQ)

[c] Unscheduled doses related to other issues will be sequentially numbered as shown

Table 10. Schedule of Assessments

Procedure	Screening	Cycle 1				Cycle 2		Cycle 3		Cycle 4 and on (every 28 days)		EOS[2]	Follow -up[3]
	(21 days)[1]	D1 (±3d)	D8 (±3d)	D15 (±3d)	D22 (±3d)	D1 (±3d)	D15 (±3d)	D1 (±3d)	D15 (±3d)	D1 (±3d)	D15 (±3d)		
Consent	X												
Medical history	X												
Cytology/pathology/mol. conf.[4]	X												
Physical exam[5], vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG perf. status	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[6]	X			X		X		X		X		X	
LE Doppler Ultrasound	X												
ECHO or MUGA[7]	X					X						X	
CBC with differential[8]	X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive metab. panel[8]	X	X	X	X	X	X	X	X	X	X	X	X	
Opthalmalogic exam[9]	X							X		X		X	
PT/PTT	X			X									
Fresh tumor biopsy[10]	X			X								X	
TSH, free T4, cortisol[11]	X					X		X		X		X	
Viral Serology[12]	X												
C-reactive protein	X												
LDH	X												

CPK	X					X		X		X		X	
Ca 19-9 and/or CEA	X					X		X		X		X	
Pregnancy test[13]	X												
Urinalysis	X												
PBMC samples[14]	X			X				X				X	
Tumor response assessment[15]	X							X				X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	
Atezolizumab administration[16]		X		X		X	X	X	X	X	X		
Dispense cobimetinib		X				X		X		X			
Dispense hydroxychloroquine		X				X		X		X			
Dispense Enoxpaparin		X				X		X		X			
Review of dosing diary			X	X	X	X		X		X		X	
Survival follow-up													X
Blood sampling for PK/PD[17]		X	X	X		X							

1. Protocol-specified screening procedures that are performed as part of standard of care and within 21 days of Day 1 of Cycle 1 may be used for screening purposes. Clinical laboratory studies and baseline CT scan must be performed within the 14-day period before Day 1 of Cycle 1. Screening labs may be used for Cycle 1 Day 1 if performed within 72 hours prior to study visit.
2. The End-of-Study (EOS) visit should be scheduled within the 28-day period after the last dose of study drug and before starting any new anti-neoplastic therapy.
3. A post-study follow-up contact by phone by site staff will be conducted every 3 months during years 1 and 2, then every 6 months thereafter to obtain information on any new anti-cancer therapy received and survival status.
4. Initial diagnosis of adenocarcinoma and KRAS mutation status needs to be confirmed by a CLIA certified pathology.
5. A complete physical examination will be performed at screening. All subsequent physical examinations will be disease-specific on Cycle 1 days 1, 8, 15, 22; Cycle 2 and 3 days 1 and 15; day 1 and 15 on each subsequent cycle, and at the End-of-Study visit.
6. ECG will be performed after the patient has been in a supine position for at least 5 minutes. It will be performed at screening, cycle 1 day 15, day 1 of every subsequent cycle, and at the End-of-Study visit.
7. ECHO or MUGA scan should be performed at screening, day 1 of cycle 2, every 3 months (+ 1 week) thereafter and at the end of study visit.

8. A complete blood count with differential and comprehensive metabolic panel including glucose, calcium, albumin, total protein, sodium, potassium, CO2 (carbon dioxide, bicarbonate), chloride, BUN (blood urea nitrogen), creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase), AST (aspartate amino transferase) and bilirubin will be performed on Cycle 1 days 1, 8, 15, and 22; Cycle 2 and 3 days 1 and 15; on day 1 and 15 of each subsequent cycle, and at the End-of-Study visit.
9. An Ophthalmologic examination should be performed during the screening period, and on cycle 3 day 1 (+ 7 days), every 12 weeks (+ 7 days) thereafter, and at the End-of-Study visit if not performed within 6 weeks. The baseline exam should include: best corrected distance visual acuity (BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted), and spectral domain ocular coherence tomography (SD-OCT). Each subsequent examinations should include BCVA, VF and SD-OCT. In patients of Asian descent, it is recommended that visual field testing be performed in the central 24 degrees instead of the central 10 degrees.
10. Fresh core tumor biopsy will be performed: (1) within 14 days of starting therapy but at least three days prior to starting therapy; (2) Cycle 1 week 3 (day 15-21); and (3) If the patient allows, at progression (within 4 days of discontinuation of therapy).
11. TSH, free T4, and AM cortisol will be assessed at screening, Day 1 of each cycle starting at C2, at end of study, and as clinically appropriate.
12. At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
13. For women of child-bearing potential, a screening serum pregnancy test must be negative within 7 days of Day 1 of Cycle 1.
14. 14. Peripheral blood mononuclear cells will be collected during screening, cycle 1 day 15, cycle 3 day 1, every eight weeks (+ 7 days), and at End-of-Service visit.
15. CT scan with contrast of the chest, abdomen, pelvis or CT chest and MRI of abdomen/pelvis, PET/CT, or appropriate imaging of disease site to assess tumor status will be performed. Imaging should be performed at the designated time for tumor assessment +/- 7 days. End of study needs not be performed if patient has radiological evidence confirming progression, but needs to be performed if patient coming off study for other reasons, except due to fatality.
    Phase 1 –Imaging to be performed every 8 weeks (+ 7 days)
    Phase 2 – Pancreas adenocarcinoma –Imaging to be performed every 8 weeks (+ 7 days)
    Colorectal adenocarcinoma – Imaging to be performed every 12 weeks (+ 7 days)
    Histology agnostic adenocarcinoma – Imaging to be performed every 8 weeks (+ 7 days)
16. The initial dose of atezolizumab will be delivered over 60 (+/- 15) minutes. Subsequent infusions will be delivered over 30 (+/-10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (+/- 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.
17. For pharmacokinetic (PK) analysis, whole blood for hydroxychloroquine and plasma for cobimetinib will be obtained on –
    Cycle 1 Day 1 - Pre-morning dose, 1, 2, and 4 hours post-morning dose.
    Cycle 1 Day 8 - Pre-morning dose, 1, and 4 hours post-morning dose.
    Cycle 1 Day 15- Pre-morning dose, 1, and 4 hours post-morning dose.
    Cycle 2 Day 1 - Pre-morning dose, 1, and 4 hours post-morning dose.

12. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for progression, as indicated in the schedule of assessments.

12.1 Treatment Beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudo-progression (Hales et al., 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Because of the potential for a response after pseudo-progression, this study will allow patients randomly assigned to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression, per immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), provided the benefit-risk ratio is judged to be favorable by the investigator in consultation with the Principal Investigator, and they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data;
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal recurrence of disease;
- Absence of decline in ECOG Performance Status that can be attributed to disease recurrence;
- Absence of tumor recurrence at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions;
- Patient's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial apparent disease recurrence.

12.2 Rationale for the Use of Immune-Modified RECIST

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization [WHO] criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression (or in this case, disease recurrence) does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ immune-modified RECIST for tumor assessments to account for the possible appearance of new lesions and allow radiographic recurrence to be confirmed at a subsequent assessment. It is required that radiographic recurrence be confirmed at a subsequent

tumor assessment to take into account the potential for pseudo-recurrence (caused by immune cell infiltration). Given the proposed immunomodulatory mechanism of action of atezolizumab, and the possibility of observing delayed responses, use of immune-modified RECIST will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described here, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al., 2009) in the same manner that immune- related response criteria were adapted from WHO criteria (Wolchok et al., 2009) and RECIST v1.0 (Nishino, Hatabu, Johnson, & McLoud, 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 11.

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

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and to allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1), in the same manner that immune-related response criteria were adapted from WHO criteria and RECIST v1.0 (Hanzelmann et al., 2013; Ritchie et al., 2018). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 11.

Table 11. Comparison of RECIST v1.1 and Immune-Modified RECIST

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

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
[1]Tumor burden is the sum of diameters of target lesions and measurable new lesions.

12.4 Tumor measurability

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable, as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment time points. Additional assessments may be performed as clinically indicated when recurrence is suspected.

12.4.1 Definition of measurable lesions

12.4.1.1 Tumor Lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval ≤ 5 mm);
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray.

12.4.1.2 Malignant Lymph Nodes

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

12.4.2 Definition of non-measurable lesions

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

12.4.3 Special considerations regarding tumor measurability

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

12.4.3.1 Bone Lesions:

- Technetium-99m bone scans, sodium fluoride PET scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques, such as CT scan or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

12.4.3.2 Cystic Lesions:

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

12.4.3.3 Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area or in an area patiented to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

12.4.4 Methods for assessing lesions

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

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

12.4.4.1 Clinical lesions

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

12.4.4.2 Chest X-ray

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

12.4.4.3 CT and MRI scans

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast

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

12.4.4.4 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 recurrence (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progressive disease (PD) based on a new lesion.
- 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 scan, this is PD, which should be confirmed by a biopsy. 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.
- FDG-PET may be used to upgrade a response to a complete response (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 that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4.4.5 Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, histology

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

12.4.5 Assessment of tumor burden

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

12.4.6 Definition of target and non-target lesions

Baseline scan should be that which is considered optimal for the particular histology.

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

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

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

12.4.7 New lesions

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

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

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

12.4.8 Calculation of sum of diameters

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

12.4.8.1 Measuring Lymph Nodes

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

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

12.4.8.2 Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non-lymph node) should have their actual measurements recorded at each subsequent evaluation,

even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

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

12.4.8.3 Measuring lesions that split or coalesce on treatment

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

12.4.8.4 Evaluating non-target lesions and non-measurable new lesions

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

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of 5 total or 2 per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

12.5 Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If measurements are made on only a subset of target or measurable new lesions at a time point, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned time point response. This would be most likely to happen in the case of treatment beyond recurrence. For example, if a patient had a recurrence sum of 50 mm with three measured lesions, and during the study only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved confirmed recurrence status, regardless of the contribution of the missing lesion.

12.6 Special notes on response assessment

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

12.7 Definitions

Evaluable for toxicity: All Participants will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response: Only those Participants 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 Participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 or who die prior to tumor assessment will also be considered non- responders).

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with 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 are not considered measurable.***

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥ 10 to <15 mm 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 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, and 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 that 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.

12.8 Response Criteria

12.8.1 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.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of 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 (including 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. (Note: 1 or more new lesions is also considered progression).

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

12.8.2 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 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 Principal Investigator.

12.9 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 (Tables 12-13).

Table 12. Response assignment for participants with measurable 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: Participants 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.

Table 13. Response assignment for participants with non-measurable 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

12.10 Duration of Response

12.10.1 Duration of overall response

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

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

12.10.2 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.

12.11 Progression-Free Survival (PFS)

Progression-free survival is defined as the duration from start of treatment to time of progression or death, whichever occurs first.

12.12 Unblinding Procedures

N/A

13. DATA REPORTING / REGULATORY REQUIREMENTS

A list of adverse events (AEs) can be found in Appendix 1. Guidelines, and instructions for AE reporting can be found in Section 10. The Data Safety Monitoring Plan is described in Section 14.3.

13.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities, and is web-based and housed on a server in a fully HIPAA-compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of Participants via an interface with the electronic medical patient index. Staff with the appropriate IRB-defined roles can run reports within the system for reporting purposes.

13.2 Data Reporting

Case Report Forms will be completed for each subject enrolled in the clinical study through the CTMS. It is the investigator's responsibility to ensure that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate, and authentic.

13.2.1 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits, and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts should be documented in the participant's medical record or study file;
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

13.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently-approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC, based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the Sponsor/Principal Investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study of the DSMC's conclusion with respect to progress or need for modification of the protocol.

13.4 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion, according to site policies and procedures.

The monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.5 Clinical Monitoring

An ssDSMP is required for all investigator initiatied trials, wherein CUIMC HICCCC DSMC is serving as the DSMC of record.

Ongoing monitoring of the clinical study for protocol and GCP compliance will be conducted on a quarterly basis by the CPDM Compliance Core on behalf of the HICCC DSMC. Quarterly

monitoring will ensure data quality and verify source documents for all enrolled subjects related to dose limiting toxicity, all response assessments and RECIST/imRECIST forms, study drug administration including, but not limited to pill accountability, duration of response, date of disease progression, resolution of treated related AEs, subsequent treatments, and survival. This report will be submitted to the Sponsor-Investigator and study statistician on a quarterly basis. Delinquent or discrepant data will be rectified within 4 weeks of notification and the quarterly report amended and resubmitted by the DSMP office. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. This trial will utilize a study-specific Data Safety Monitoring Plan (which is to be reviewed and acknowledged by the HICCC DSMC).

The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

13.5.1 Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
- The Compliance Coordinator will communicate with the site coordinator/site Principle Investigator to schedule the monitoring visits and arrange for access to study materials and documentation.
- In accordance with the ssDSMP and RBM methologies, the assigned Compliance Coordinator will monitor IIT trials throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible for notifying the PI and CRNP/CRN/CRC of upcoming monitor visits, and for conveying what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies, as appropriate.

13.5.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study;
- Who will have access to that information and why;
- Who will use or disclose that information;
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

13.5.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Source documents including, but not limited to, those needed to establish subject eligibility, response scans, dose limiting toxicity, imRECIST, and pill accountability will be made available to the Principal Investigator on at least a quarterly basis.

13.5.4 Data Entry Procedures

The Herbert Irving Comprehensive Cancer Center has an electronic CTMS that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA-compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Patient data is entered directly into the

system, which (in the case of Columbia patients) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB-defined roles can run reports within the system for reporting purposes.

13.5.5 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least 3 years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least 2 years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least 2 years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least 7 years, per CUMC and NYP policy, which is based on state law.

14. TRANSLATIONAL SCIENCE

14.1.1 PDAC Subtypes as Defined by Immune Cell Infiltrate and Gene Expression

14.1.1.1 $CD8^+$ T-Cell Infiltration and Survival

$CD8^+$ TILs, which are known anti-tumor effector cells, are less frequently found in the PDA tumor microenvironment (TME) as compared to the more 'inflamed' TMEs of melanoma, non-small cell lung cancer (NSCLC), or renal cell carcinoma (RCC) (Vonderheide & Bayne, 2013). In part, this may be explained by the unique desmoplastic stroma that typically surrounds PDAC epithelial cells. This has been hypothesized to act as a physical barrier to T-cell infiltration, but recent data has challenged this theory (Carstens et al., 2017; Ene-Obong et al., 2013). The PDA stroma is typically infiltrated by significant numbers of immunosuppressive leukocytes, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T-cells (Clark et al., 2007; Hiraoka, Onozato, Kosuge, & Hirohashi, 2006) . Recent evidence has surfaced supporting a correlation between increased $CD8^+$ lymphocyte infiltration and improved prognosis, suggesting $CD8^+$ infiltration may serve as a good surrogate for response to therapy (Cheng, Sato, Kohi, & Yamaguchi, 2013; Deng et al., 2016). In an effort to better-characterize the TME of solid tumors, several novel technologies have been developed. Quantitative multiplex immunofluorescence (qmIF) represents one such platform and allows for simultaneous identification of multiple distinct epitopes on a single formalin-fixed, paraffin-embedded tissue section using a unique tyramide signal amplification technique (Stack, Wang, Roman, & Hoyt, 2014). This technology is only available at a few institutions and is rapidly becoming an accepted method for studying the TME in many cancers (Carstens et al., 2017; Schalper et al., 2015; Tumeh et al., 2014). Using qmIF, Carstens et al. demonstrated that high

infiltration of $CD8^+$ and $CD4^+$ T-cells correlated with improved survival, whereas infiltration of regulatory T cells or other T cell subtypes was not. In addition, increased infiltration of intra-tumoral $CD8^+$ T cells within a 20μM radius of tumor cells also correlated with prolonged patient survival (Deng et al., 2016). An example of work performed at Columbia University Irving Medical Center (CUIMC) is shown in Figure 6.

14.1.2 VECTRA Imaging of Human PDA

A detailed protocol of tissue processing is provided in the laboratory manual. After the Manji laboratory has been contacted and approval given, tissue samples are to be sent to the address below to ensure receipt and processing on delivery. Specimens should be shipped either on a Monday or Tuesday of a non-holiday week to accommodate possible shipment delays and ensure timely delivery of biospecimens.

Attention to:

Gulam Abbas Manji, MD/PhD
Herbert Irving Comprehensive Cancer Center Columbia University
1130 Saint Nicholas Avenue, ICRC 207 New York, NY 10032
Phone: 212-304-6357
Alternate: 518-488-4704

14.1.3 Laser Capture Microdissection (LCM) and PDA

We believe that the combinations being tested, including atezolizumab, hydroxychloroquine, and cobimetinib, will change the regulatory context of the PDAC TME from an immunotherapy-resistant to an immunotherapy-sensitive phenotype. Fresh frozen tissue will be sectioned for laser capture microdissection of the neoplastic epithelial and stromal components for RNA extraction.

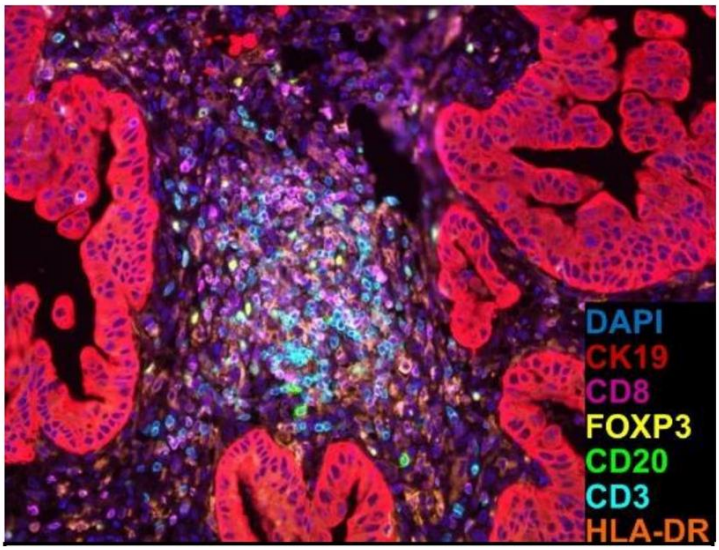

Figure 6. VECTRA imaging of human PDA.
7-color IP: DNA (DAPI), cytotoxic T-cells (CD8), macrophage (CD68), helper T-cells (CD4), regulatory T-cells (FOXP3), pan-T-cells (CD3), and proliferation (Ki67).

PDAC are characterized by two main components: the epithelium, formed from aggregates of tumor cells, and the surrounding stroma. Moffitt et al. (2015) performed virtual microdissection on gene expression microarray data obtained from 145 PDA patients, and identified two distinct epithelial-specific subtypes. One

subtype contained genes enriched for extracellular matrix (ECM) deposition and remodeling, which they termed 'basal-like', while the other was enriched in immune and interleukin pathways, termed 'classical'. Distinct gene signatures represented by 25 distinct genes were able to distinguish these two phenotypes. The classical molecular subtype represented a patient population with an improved median OS compared to that of the basal-like subtype (Moffitt et al., 2015).

The Olive lab here at CUIMC has performed LCM on over 200 human pancreatic tumors and RNA-seq to a depth of 30 million 100 base pair single-end reads. Their analyses showed clean separation of the two compartments. Hierarchical clustering, using Neutral Matrix Factorization of the top 1000 variable genes of the stromal RNA-seq data, found two distinct clusters. One cluster was enriched for inflammatory genes, while the other was enriched in both immune effector and immunosuppressive signatures; these groups were classified "classical" and "basal-like" subtypes, respectively [Kenneth Olive, submitted]. Furthermore, supervised clustering analysis of the RNA-seq data, using the same epithelial classifier signatures described by Moffitt et al., confirmed the prognostic value of PDA molecular subtypes in the CUMC cohort. As shown in Figure 7, patients with the classical epithelial phenotype have significantly better prognoses as compared to those with the basal-like phenotype [Kenneth Olive, submitted].

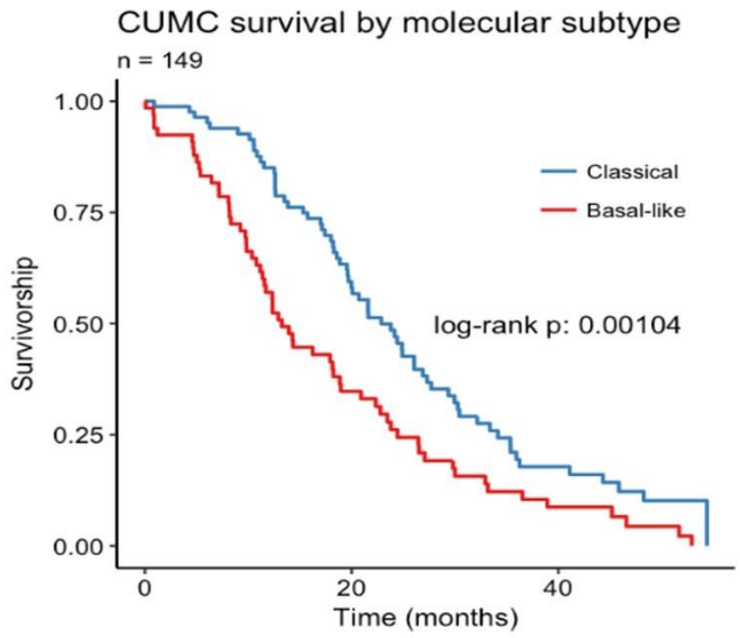

Figure 7. Kaplan-Meier survival by molecular subtype.
VECTRA imaging of human PDA. Analysis of RNA-seq data from patients with resected

We hypothesize that the combination of atezolizumab, hydroxychloroquine, and cobimetinib, will result in gene regulation that enriches the immune and interleukin pathways, which reflect classical/immune subtype compared to the basal-like/ECM subtype. In order to test this hypothesis, the epithelium compartment will be isolated using LCM from each resected tumor specimen on which RNA-seq analysis will be performed. Using epithelial classifiers, as described above, samples from distinct treatment groups will be compared to determine if certain treatments are able to alter the PDA epithelial gene expression from 'basal/ECM-like' to 'classical/immune' subtype, which may confer a prognostic advantage. If a treatment(s) leads to enrichment of classical/immune subtype and improved outcomes, the regulated pathways that associate with improved disease-free survival will need to be validated in a larger sample, and those pathways further exploited to convert the tumor into one that is

more susceptible to immunotherapy. These studies will complement the multiplex immunofluorescence (IF) studies described above and will hopefully identify key regulatory pathways affected by distinct therapies.

14.2 Sample Processing of RNA-Seq Expression Data

A detailed protocol of tissue processing is provided in the laboratory manual. Briefly, fresh frozen tissue will be obtained from EUS-guided biopsy and surgically resected tissue and immediately sectioned and microscopically evaluated. Suitable samples will be transferred into OCT medium (Tissue Tek) and snap frozen in a 2-methylbutane dry ice slurry. The tissue blocks will be stored at -80^{o}C until further processing at Manji's laboratory, as per established protocol. Frozen blocks are to be sent to Dr. Manji's laboratory using the address listed below after the laboratory has been contacted and approval given to ship the specimens to ensure receipt and processing on delivery. Specimens should be shipped either on a Monday or Tuesday of a non-holiday week to accommodate possible shipment delays and ensure timely delivery of biospecimens.

Attention to:

Gulam Abbas Manji, MD/PhD
Herbert Irving Comprehensive Cancer Center Columbia University
1130 Saint Nicholas Avenue, ICRC 207 New York, NY 10032
Phone: 212-304-6357
Alternate: 518-488-4704

15. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB-approved protocol, and the investigator-designated research professional obtaining the consent.

16. STUDY FINANCES

16.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict

reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

17. GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

17.1 Multi-Site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate regularly scheduled conference calls with affiliate sites.

The following issues will be discussed, as appropriate:

- Enrollment information;
- Cohort updates (e.g., DLTs);
- Adverse events (e.g., new AEs and updates on unresolved AEs and new safety information);
- Protocol violations;
- Other issues affecting the conduct of the study.

17.2 New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol-specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site-specific revisions to protocol and/or consent form documents for review and approval by the Sponsor Investigator prior to submission to the local IRB. Draft documents should be sent to the study−specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the Sponsor-Investigator.

17.3 Regulatory Documents

17.3.1 Prior to Site Initiation:

The Sponsor Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- Curriculum vita (CV) of site's Principal Investigator, Co-Investigators, and other research staff listed on FDA 1572 (signed and dated copy within 2 years);

- Medical licenses of PI and Co-Investigators (current copy);
- Human patients training certificates for Principal Investigator and Co-Investigators;
- CLIA/laboratory certifications for local laboratories listed on FDA 1572;
- Local laboratory Director's CV and license;
- Local laboratory reference ranges;
- IRB roster or statement of compliance;
- FDA Form 1572, if applicable (wet ink originals required);
- Financial disclosure forms for all members listed on FDA 1572 (wet ink originals required).

17.3.2 Ongoing Regulatory Documentation

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study:

- IRB approval letters for all protocol modifications and all renewals;
- IRB-approved consent forms;
- Current IRB roster, if statement of compliance is not provided as part of site initiation;
- FDA Form 1572, if applicable as updates are required;
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information).

Regulatory documents may be sent to AAAS4165@lists.cumc.columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

17.4 Site Activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

17.5 Central Registration Procedures--Affiliate Institution Research Participant Registration Process

All Affiliate Institutions **must** register patients with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's Multicenter Core and the study email AAAS4165@lists.cumc.columbia.edu. The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email with a request to register the patient "pending eligibility". The title of the email should read, "AAAS4165 Pending Patient Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    - Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable;
    - Redacted Signed HIPAA (or institutional equivalent);
    - MCT CPDM Velos Note to File form.
2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC Multicenter Core) via telephone or email to communicate the following:
    - Notify of pending registration request
    - Confirm method of registration request submission (email or fax)
    - Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)
3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC Multicenter Core/designee:
    - A signed Affiliate Site Eligibility Checklist (signed by the investigator);
    - Copies of redacted source documentation necessary for each item to be verified on the CUMC-specific Eligibility Checklist, including but not limited to:
        - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.);
        - Copy of pathology and surgical reports;
        - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for

screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.).

Please note: subject line of email or fax should include the following: "**AAAS4165** Complete Patient Registration Request (PHI)".

4. Upon receipt of the above-mentioned documents, the designated study-specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study-specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study-specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications as necessary prior to enrollment.
5. Upon receipt of the patient registration notification email, the CUMC study-specific designee will forward the notification email (which will include the study-specific patient ID) to the affiliate site's PI, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy may not be initiated prior to receipt of this notification from the coordinating center.
6. All screen-fail/ineligible patients, as well as patients who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

17.6 Protocol Deviation request for Affiliate Sites:

The Affiliate site **must** submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB deviation approval letter(s) should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation. All documents and determinations must be clearly documented in the study patient's medical record, research chart, and regulatory binder, as described.

The HICCC DSMC and PRMC will no longer accept eligibility deviations, but will still continue to accept deviations not related to eligibility.

17.7 Guidelines for Affiliate Site Monitoring

17.7.1 On-Site MCT Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
- The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
- The Compliance Coordinator will monitor IIT trials within 1 month after the first patient is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRFs accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported, according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies, as appropriate.
- A site initiation visit (SIV) (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any patients are enrolled on a study at the Affiliate site.

17.7.2 Remote MCT Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site-by-site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.

- Redacted source documents (applicable to supporting the protocol−specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all patients enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case-by-case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    - Informed consent procedures;
    - Eligibility criteria;
    - Protocol-specific treatment compliance;
    - Protocol-specific toxicity/outcome documentation/compliance;
    - Protocol-specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up);
    - Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, IND Safety Reports submissions, etc.);
    - Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.);
    - Pharmacy accountability records; and
    - Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes).
- Affiliate site remote monitoring reports will be sent to the lead Principal Investigator, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

17.8 Adverse Event Reporting

17.8.1 Sponsor Reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study Sponsor to notify all affiliate sites, in a written IND safety report, of any AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human patients. Additionally, Sponsors are also required to identify in IND safety reports all previous reports concerning similar AEs, and to analyze the significance of the current event in light of the previous reports.

17.8.2 Sub-Site SAE Reporting Procedures:

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the Principal Investigator.

Participating investigators must report each SAE to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the SAE **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE. Report SAEs by telephone, email, or facsimile to:

Gulam Abbas Manji, M.D/Ph.D.
161 Fort Washington Avenue
New York, NY 10032
Telephone: 212-304-6357 (Multicenter Trial Number)
Fax: 212-304-6330 (Multicenter Trial Fax)
Email: CPDM Multicenter Trials Core (AAAS4165@lists.cumc.columbia.edu)

The participating investigator must provide follow-up information on the SAE until resolution of the event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation, and if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the Sponsor-Investigator may urgently require further information from the investigator for reporting to Health Authorities.

17.8.3 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall PI on the toxicity Case Report Forms.

17.9 Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All UPs will be reported to the CUMC IRB. SAEs not constituting UPs will be reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

17.10 Guidelines for Processing IND Safety Reports

The FDA regulations require Sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly to forward the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site IND Safety Reports submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

17.11 Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any patient safety reports or sentinel events that require reporting according to institutional policy.

17.12 Confidentiality

Each affiliate site will be assigned a site number. Each patient that signs consent should be assigned a unique code number consisting of site number followed by a number with each new patient being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Patient confidentiality must be maintained according to HIPAA regulations and GCP recommendations. Except when required by law, study information shared with persons and organizations outside of CUMC must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting, the patient must not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

17.13 Data Reporting Plan

CUMC is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the PI, Statistician, Data Safety and Monitoring Board (DSMB), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Patients.

17.14 Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all patients prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

17.15 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by patients, as well as written records of the disposition of the drug when the study ends.

The PI is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the

case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

18. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

19. REFERENCES

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20. ATTACHMENTS

None

21. APPENDICES

21.1 Appendix 1: Management of adverse events while administering atezolizumab, cobimetinib, and/or hydroxychloroquine

Table A1.1. Guidelines for managing IRRs, anaphylaxis, and hypersensitivity reactions in response to **a*tezolizumab, cobimetinib, and/or hydroxychloroquine*.**

Event	Action
IRR, Grade 1	• Reduce infusion rate to half the rate at time of event onset, and continue for 30 min; • If the reduced rate infusion is tolerated for 30 min after symptoms have resolved, resume infusion at higher rate.
IRR, Grade 2	• Interrupt infusion; • Administer aggressive symptomatic treatment (e.g., oral/IV antihistamine, epinephrine, oxygen); • After symptoms have resolved, resume infusion at half rate; • Administer oral premediation with antihistamine and anti-pyretic prior to subsequent infusions and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion; • Administer aggressive symptomatic treatment (e.g., oral/IV antihistamine, epinephrine, oxygen); • Permanently discontinue the drug and contact PI.

Table A1.2. Guidelines for managing gastrointestinal events in response to ***atezolizumab, and/or cobimetinib*.**

Event	Action
General guidance	• All GI events should be evaluated for more common etiologies; • For events of significant duration or magnitude, perform sigmoidoscopy (or colonoscopy) with colonic biopsy to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis; • Administer all anti-diarrheal agents and other supportive care per institutional guidelines.
Diarrhea or colitis, Grade 1	• Continue atezolizumab (if applicable) and cobimetinib; • Initiate symptomatic treatment; • Recommend endoscopy if symptoms persist >7 days; • Monitor closely.

Diarrhea or colitis, Grade 2-3	• Withhold atezolizumab (if applicable) and cobimetinib;
	• Initiate symptomatic treatment;
	• Discontinue medications that may exacerbate colitis while investigating etiology;
	• Refer patient to GI specialist (recommended);
	• If Received Atezolizumab –
	  • If event recurs, or persists >5 days, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent.
	  • Resume atezolizumab at fixed dose

	if event resolves to Grade 1 or better within 12 weeks; • Resume Cobimetinib with dose reduced by 1 level if event resolves to Grade 1 or better within 28 days • If event does not resolve, permanently discontinue atezolizumab (if applicable) and cobimetinib and contact PI.
Diarrhea colitis, Grade 4	• Permanently discontinue atezolizumab (if applicable) and cobimetinib and contact PI; • Refer patient to GI specialist (confirmation and biopsy); • Discontinue medications that may exacerbate colitis while investigating etiology; • If Received Atezolizumab – • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. Convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement; • If event does not improve within 48 hrs after starting corticosteroids, consider immunosuppressive agent; • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Table A1.3. Guidelines for managing dermatologic events in response to ***atezolizumab, cobimetinib, and/or hydroxychloroquine***

Event	Action
General guidance	• Seek dermatologic evaluation for persistent and/or severe rash or pruritis • Consider biopsy unless contraindicated
Grade 1 or 2	• Continue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine • Initiate supportive care. If event does not improve, consider treatment with higher potency topical steroids. • For Grade 2, consider referral to dermatologist • For acneiform rash: consider initiating treatment with topical corticosteroids and oral antibiotics, as clinically indicated.
Grade 3	• Withhold atezolizumab (if applicable), cobimetinib, and hydroxychloroquine; • Refer patient to dermatologist; • If Received Atezolizumab – • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, discontinue atezolizumab and cobimetinib and contact PI. • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by 1level. If not, permanently discontinue cobimetinib. • For acneiform rash: consider initiating treatment with topical corticosteroids and oral antibiotics, as clinically

	indicated.
Grade 4	• Permanently discontinue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine and contact PI.

Table A1.4. Guidelines for managing hepatic events in response to ***atezolizumab, cobimetinib, and/or hydroxychloroquine***

Event	Action
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > 3xULN with total bilirubin >ULN to ≤ 2xULN	• Continue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine, and contact PI.

AST/ALT > 3 x ULN to 5 x ULN with total bilirubin > ULN to ≤ 2xULN	• Continue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine, and contact PI.
	• Monitor LFT weekly;
	• Consider referral to hepatologist and liver biopsy;
	• If Received atezolizumab –
	  • For suspected immune-related events lasting >5 days:
	  o Consider withholding atezolizumab;
	  o Consider initiating 1-2mg/kg/day prednisone or equiv.;
	  o If atezolizumab is withheld and event resolves to AST/ALT ≤ 2 x ULN within 12 weeks, resume at fixed dose. Otherwise, discontinue atezolizumab and cobimetinib, and contact PI.[a,b,c]

AST/ALT > 5 x ULN to < 10 x ULN with total	• Continue atezolizumab (if applicable),

bilirubin > ULN to ≤ 2xULN	cobimetinib, and hydroxychloroquine, and contact PI. • Monitor LFT weekly; • Consider referral to hepatologist and liver biopsy; • If Received Atezolizumab – • For suspected immune-related events lasting >5 days: o Consider withholding atezolizumab; o Consider initiating 1-2mg/kg/day prednisone or equiv.; o If atezolizumab is withheld and event resolves to AST/ALT ≤ 2 x ULN within 12 weeks, resume at fixed dose. Otherwise, discontinue atezolizumab and cobimetinib, and contact PI.[a,b,c]
AST/ALT > ULN to ≤ 3 x ULN with total bilirubin > 2 x ULN	• Investigate causes for elevated bilirubin and initiate treatment per institutional guidelines; • Use best medical judgement as to whether to continue study treatment.
AST/ALT > 3 x ULN with total bilirubin > 2 x ULN	• Withhold atezolizumab (if applicable), cobimetinib, and hydroxychloroquine. • Monitor LFTs every 48-72 hrs until decreasing; then monitor weekly. • Refer to hepatologist and consider liver biopsy. • If Received atezolizumab – • Consider initiating 1-2 mg/kg.day oral prednisone treatment (or equivalent). • If corticosteroids are initiated and event does not improve within 48 hrs,

	consider adding immunosuppressive agent. • If event resolves to AST/ALT ≤ 2 x ULN within 12 weeks, resume at fixed dose. Otherwise, discontinue atezolizumab and cobimetinib, and contact PI.[a,b,c] • If event resolves to AST/ALT ≤ 2 x ULN within 28 days, resume cobimetinib and hydroxychloroquine with dose reduced by one level. If not, premanently discontinue cobimetinib and hydroxychloroquine. • Permanently discontinue atezolizumab, cobimetinib, and hydroxychloroquine for life-threatening hepatic events and contact the PI.
AST/ALT > 10 x ULN	• Permanently discontinue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine and contact PI. • Monitor LFTs every 48-72 hrs until decreasing; then monitor weekly. • Refer to hepatologist and consider liver biopsy. • If Received atezolizumab – • Consider initiating 1-2 mg/kg.day oral prednisone treatment (or equivalent). • If corticosteroids are initiated and event does not improve within 48 hrs, consider adding immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 x ULN with total bilirubin ≤ 2 x ULN,

	taper corticosteroids over ≥1 month.
LFT = liver function test; ULN = upper limit of normal. [a] Corticosteroids must be tapered over ≥1 month to ≤ 10 mg/kg/day oral prednisone or equivalent before atezolizumab may be resumed. [b] Atezolizumab may be withheld for more than 12 weeks to allow for corticosteroid treatment tapering. Course must be agreed upon by the investigator and PI. [c] Resuming atezolizumab may be considered in patients who are deriving benefit an have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval from both the investigator and the PI.	

Table A1.5. Guidelines for managing pulmonary events in response to ***atezolizumab*, and/or cobimetinib.**

Event	Action
General guidance	• All pulmonary events would be thoroughly evaluated for other commonly reported etiologies.
Grade 1	• Continue atezolizumab (if applicable) and cobimetinib. • Re-evaluate on serial imaging; • Consider referral to pulmonary specialist;
Grade 2	• Withhold atezolizumab (if applicable) and cobimetinib. • Refer patient to pulmonary and infectious disease specialist; • Consider bronchoscopy or BAL; • If results are consistent with immune-related etiology or pneumonitis, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent; • Resume atezolizumab (if applicable) at fixed dose if event resolves to Grade 1 or better within 12 weeks;

	• If event does not resolve, permanently discontinue atezolizumab (if applicable) and cobimetinib and contact PI.[a,b,c] • Treat recurrent events as Grade 3 or 4.
Grade 3 or 4	• Permanently discontinue atezolizumab (if applicable) and cobimetinib and contact PI.[c] • Bronchoscopy or BAL is recommended; • If results are consistent with immune-related etiology or pneumonitis, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hrs, or worsens, after starting corticosteroids, consider immunosuppressive agent; • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
BAL = brochoscopic alveolar lavage [a] Corticosteroids must be tapered over ≥1 month to ≤ 10 mg/kg/day oral prednisone or equivalent before atezolizumab may be resumed. [b] Atezolizumab may be withheld for more than 12 weeks to allow for corticosteroid treatment tapering. Course must be agreed upon by the investigator and PI. [c] Resuming atezolizumab may be considered in patients who are deriving benefit an have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval from both the investigator and the PI.	

Table A1.6. Guidelines for managing endocrine disorders in response to ***atezolizumab, and/or cobimetinib.***

Event	Action
Asymptomatic hypothyroidism	• Continue atezolizumab (if applicable) and cobimetinib; • Initiate thyroid hormone replacement treatment; • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab (if applicable); • Continue cobimetinib; • Initiate thyroid replacement hormone treatment; • Monitor TSH weekly; • Consider referral to endocrinologist; • Resume treatment when symptoms are controlled and thyroid function is improving.
*Asymptomatic hyperthyroidism	If TSH ≥0.1mU/L and <0.5 mU/L: • Continue atezolizumab (if applicable) and cobimetinib; • Monitory TSH every 4 weeks. If TSH <0.1mU/L Follow guidelines for symptomatic hyperthyroidism;
Symptomatic hyperthyroidism	• Withhold atezolizumab (if applicable); • Continue cobimetinib; • For life-threatening immune-related hyperthyroidism, withhold

	cobimetinib. If event becomes clinically manageable within 28 days, resume cobimetinib with dose reduced 1 level. If not, permanently discontinue cobimetinib. • Initiate treatment with anti-thyroid drug, such as methimazole or carbimazole, as needed; • Consider referral to endocrinologist; • Resume treatment when symptoms are controlled and thyroid function is improving; • If condition is life-threatening, permanently discontinue atezolizumab (if applicable) and contact PI.
Symptomatic adrenal insufficiency, Grade 2-4	• Withhold atezolizumab (if applicable); • Continue cobimetinib. • Refer patient to endocrinologist; • Perform appropriate imaging; • If Received atezolizumab – • Initiate 1-2 mg/kg/day IV methylprednisolone or equivalent; convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement; • Resume atezolizumab (if applicable) treatment if event resolves to Grade 1 or better within 12 weeks; • If event does not resolve to Grade 1 or better within 12 weeks, or patient is not stable on replacement therapy, permanently discontinue atezolizumab (if applicable) treatment and contact PI.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab (if applicable) and cobimetinib;

	• Initiate treatment with insulin, as needed; • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab (if applicable); • Continue cobimetinib. • Initiate treatment with insulin; • Monitor for glucose control; • Resume atezolizumab (if applicable) when symptoms resolve and glucose levels are stable.
TSH = tyhyroid stimulating hormone [a] Corticosteroids must be tapered over ≥1 month to ≤ 10 mg/kg/day oral prednisone or equivalent before atezolizumab may be resumed. [b] Atezolizumab may be withheld for more than 12 weeks to allow for corticosteroid treatment tapering. Course must be agreed upon by the investigator and PI. [c] Resuming atezolizumab may be considered in patients who are deriving benefit an have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval from both the investigator and the PI.	

Table A1.7. Guidelines for managing pancreatic events in response to ***atezolizumab, and/or cobimetinib.***

Event	Action
Amylase and/or lipase elevation Grade 1	• Continue atezolizumab (if applicable) and cobimetinib. • Monitor amylase and lipase prior to dosing.
Amylase and/or lipase elevation Grade 2	• Continue atezolizumab (if applicable) and cobimetinib. • Monitor amylase and lipase weekly. • For prolonged elevation (> 3 weeks), consider 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab (if applicable). • Continue cobimetinib.

	• Monitor amylase and lipase every other day.
	• If Received atezolizumab –
	  • If no improvement, consult GI and consider 1-2 mg/kg/day oral prednisone or equivalent.
	  • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a,b]
	  • Permanently discontinue atezolizumab and contact PI if event does not resolve to Grade 1 or better within 12 weeks. [a,b,c]
	  • For recurrent events, permanently discontinue cobimetinib, and contact PI.

Immune-related pancreatitis Grade 2	• Withhold atezolizumab (if applicable).
	• Continue cobimetinib.
	• Refer patient to GI specialist.
	• If Received atezolizumab –
	  • Upon improvement, initiate 1-2 mg/kg/day IV methylprednisone or equivalent. Convert to 1-2 mg/kg/day oral prednisone upon improvement.
	  • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a,b]
	  • Permanently discontinue atezolizumab and contact PI if event does not resolve to Grade 1 or better within 12 weeks. [a,b,c]
	  • For recurrent events, permanently discontinue atezolizumab, and contact PI.

Immune-related pancreatitis Grade 3	• Withhold cobimetinib.

	• Follow guidelines for atezolizumab (if applicable) for Grade 2 event.

Immune-related pancreatitis Grade 4	• Permanently discontinue atezolizumab (if applicable) and consider permanently discontinuing cobimetinib. Contact PI.[c]
	• If cobimetinib is withheld and event resolves to Grade 1 or better within 28 days, resume treatment at current dose. If event does not resolve to Grade 1 or better within 28 days, permanently discontinue treatment.
	• Refer patient to GI specialist.
	• If Received atezolizumab –
	  • Upon improvement, initiate 1-2 mg/kg/day IV methylprednisone or equivalent. Convert to 1-2 mg/kg/day oral prednisone upon improvement.
	  • If event does not improve within 48 hrs of initiating corticosteroid treatment, consider adding an immunosuppressive agent.
	  • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Corticosteroids must be tapered over ≥1 month to ≤ 10 mg/kg/day oral prednisone or equivalent before atezolizumab may be resumed.
[b] Atezolizumab may be withheld for more than 12 weeks to allow for corticosteroid treatment tapering. Course must be agreed upon by the investigator and PI.
[c] Resuming atezolizumab may be considered in patients who are deriving benefit an have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval from both the investigator and the PI.

Table A1.8. Guidelines for managing neurologic disorders in response to ***atezolizumab, cobimetinib, and/or hydroxychloroquine.***

Event	Action
Neuropathy Grade 1	• Continue atezolizumab (if applicable) and cobimetinib. • Withhold hydroxychloroquine. • Investigate etiology.
Neuropathy Grade 2	• Withhold atezolizumab (if applicable) and hydroxychloroquine; • Continue cobimetinib. • Investigate etiology. • Initiate treatment according to institutional guidelines. • Resume atezolizumab (if applicable) if event resolves to Grade 1 or better within 12 weeks. [a,b] • Permanently discontinue atezolizumab (if applicable) and contact PI if event does not resolve to Grade 1 or better within 12 weeks. [a,b,c]
Neuropathy Grade 3	• Permanently discontinue atezolizumab (if applicable) and contact PI. • Withhold hydroxychloroquine. • Continue cobimetinib. • Initiate treatment according to institutional guidelines.
Neuropathy Grade 4	• Permanently discontinue atezolizumab (if applicable) and contact PI. • Withhold cobimetinib and hydroxychloroquine. • Initiate treatment according to institutional guidelines.

	• If patient stabilizes within 28 days, consider resuming cobimetinib at current dose and resuming hydroxychloroquine at 1 dose level lower. If not, permanently discontinue treatment with these drugs.
Myasthenia gravis or Guillain-Barré syndrome, Grade 4	• Permanently discontinue atezolizumab (if applicable). • Withhold cobimetinib and hydroxychloroquine. • Refer patient to neurologist. • Initiate treatment according to institutional guidelines. • If Received atezolizumab – • Consider 1-2 mg/kg/day oral or IV prednisone or equivalent. • If patient stabilizes within 28 days, resume cobimetinib at current dose, and resume hydroxychloroquine at 1 dose level lower. If not, permanently discontinue cobimetinib and hydroxychloroquine.

Meningoencephalitis, all grades	• Permanently discontinue atezolizumab (if applicable) and contact PI. [a]
	• Withhold cobimetinib and hydroxychloroquine.
	• Refer patient to neurologist.
	• If Received atezolizumab –
	  • Initiate 1-2 mg/kg/day IV methylprednisone or equivalent. Convert to 1-2mg/kg/day oral prednisone or equivalent upon improvement.
	  • If event does not improve within

	48 hrs of initiating corticosteroids, consider adding an immunosuppressive agent. • If patient stabilizes within 28 days, resume cobimetinib at current dose, and resume hydroxychloroquine at 1 dose level lower. If not, permanently discontinue cobimetinib and hydroxychloroquine.
[a] Resuming atezolizumab may be considered in patients who are deriving benefit an have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval from both the investigator and the PI.	

Table A1.9. Guidelines for managing ocular events in response to ***atezolizumab, cobimetinib, and/or hydroxychloroquine***.

Event	Action
General guidance	• Refer patient to ophthalmologist.
Serious retinopathy, Grade 1	• Continue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine; • Refer to ophthalmologist;
Serious retinopathy, Grade 2 (tolerable)	• Continue atezolizumab (if applicable) and cobimetinib. • Withhold hydroxychloroquine. • If event resolves to Grade 1, resume hydroxychloroquine at one dose level lower. • Refer to ophthalmologist.
Serious retinopathy, Grade 2 (intolerable), Grade 3 or Grade 4	• Withhold cobimetinib and hydroxychloroquine. • Continue atezolizumab (if applicable). • Complete ophthalmologic examination. • If even improves by at least one grade

	within 28 days, resume cobimetinib and hydroxychloroquine at 1 dose level lower. If not, permanently discontinue cobimetinib and hydroxychloroquine.
Retinal vein occlusion	• Permanently discontinue cobimetinib and hydroxychloroquine. • Continue atezolizumab (if applicable). • Treatment as per institutional guidelines.
Potential immune-related ocular toxicity, Grade 1	• Continue atezolizumab (if applicable), cobimetinib, and hydroxychloroquine. • Complete ophthalmologic examination. • Initiate topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as Grade 2.
Potential immune-related ocular toxicity, Grade 2	• Withhold atezolizumab (if applicable). • Continue cobimetinib and hydroxychloroquine. • Initiate topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab (if applicable). If not, permanently discontinue atezolizumab (if applicable), hydroxychloroquine, and cobimetinib and contact PI. [a,b,c]
Potential immune-related ocular toxicity, Grade 3 or 4	• Permanently discontinue atezolizumab, cobimetinib, and hydroxychloroquine, and contact PI.[c]
[a] Corticosteroids must be tapered over ≥1 month to ≤ 10 mg/kg/day oral prednisone or	

equivalent before atezolizumab may be resumed.
[b] Atezolizumab may be withheld for more than 12 weeks to allow for corticosteroid treatment tapering. Course must be agreed upon by the investigator and PI.
[c] Resuming atezolizumab may be considered in patients who are deriving benefit an have fully recovered from the immune-related event. Patients can be re-challenged with atezolizuman only after approval from both the investigator and the PI.

Table A1.10. Guidelines for managing cardiac events in response to ***atezolizumab, cobimetinib, and/or hydroxychloroquine***.

Event	Action
Asymptomatic LVEF increase from baseline.	
LVEF ≥ 50% or LVEF 40-49% with <10% absolute decrease from baseline	• Continue cobimetinib, atezolizumab (if applicable), and hydroxychloroquine.
LVEF < 40% or LVEF 40-49% with ≥ 10% absolute decrease from baseline	• Withhold cobimetinib and hydroxychloroquine. Continue atezolizumab (if applicable) as clinically indicated. • Reevaluate LVEF at 14 days. • If patient has <10% absolute decrease from baseline LVEF, resume cobimetinib and hydroxychloroquine with dose level reduced by 1. Reevaluate after 2, 4, 10, and 16 weeks, and then every 12 weeks thereafter, or as clinically indicated. • If patient has LVEF <40% or a ≥ 10% absolute decrease from baseline, permanently discontinue cobimetinib and hydroxychloroquine. Assess LVEF every 6 weeks, or as clinically indicated, until LVEF recovers to 50% or lower limit of normal.
Symptomatic LVEF decrease from baseline	• Withhold cobimetinib and hydroxychloroquine for at least 4 weeks. • Consider withholding atezolizumab (if applicable). • Refer patient to cardiologist. • If atezolizumab is withheld (if applicable), contact the PI to discuss

	resuming treatment.
	• Reevaluate LVEF at 28 days.
	• If patient is asymptompatic after treatment break:
	  o Resume cobimetinib and hydroxychloroquine with dose reduced 1 level if <10% absolute decrease from baseline LVEF.
	  o Permanently discontinue cobimetinib and hydroxychloroquine if <40% or ≥10% asolute decrease from baseline. Continue to assess LVEF every 6 weeks.
	• If patient is symptomatic following treatment break, permanently discontinue cobimetinib and hydroxychloroquine. Assess LVEF every 6 weeks until LVEF recovers to 50% or to the lower limit of normal, or until symptoms resolve.

Rhabdomyolysis or CPK elevation	
General guidance	• Evaluate for cardiac cause and rhabdomyolysis. • Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
Asymptomatic CPK elevation, Grade 1-3	• Continue atezolizumab (if applicable) and cobimetinib. • Recheck CPK at least 1/wk
Asymptomatic CPK elevation, Grade 4	• Withhold atezolizumab (if applicable), cobimetinib, and hydroxychloroquine.

	• If resolved to Grade 3 or better within 28 days, resume cobimetinib and hydroxychloroquine with dose reduced by one level. If not, permanently discontinue cobimetinib and hydroxychloroquine. [a]
Rhabdomyolysis or symptomatic CPK elevation	• Withhold atezolizumab (if applicable), cobimetinib, and hydroxychloroquine. • If symptoms improve by at least one grade within 28 days, resume cobimetinib and hydroxychloroquine with dose level reduced by one. If not, permanently discontinue cobimetinib and hydroxychloroquine.[a]
[a] Resuming atezolizumab (if applicable) may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only	

Table A1.11. Guidelines for managing hemorrhage and other toxicities in response to ***atezolizumab and/or cobimetinib.***

Event	Action
Hemorrhage Note: There are no clinical data on the effectiveness of cobimetinib dose modifications for hemorrhage events	
Grade 3 hemorrhage other than cerebral hemorrhage	• Withhold cobimetinib. • Continue atezolizumab (if applicable). • If cobimetinib cannot be resumed within 28 days, permanently discontinue.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Permanently discontinue cobimetinib if event is attributed to the drug. Otherwise, withhold cobimetinib. • Continue atezolizumab (if applicable).
Atezolizumab-related toxicities not described above (if applicable)	
Grade 1	• Continue atezolizumab (if applicable) and cobimetinib.
Grade 2 (intolerable)	• Withhold atezolizumab. • Continue cobimetinib. • If event resolves to Grade 1 within 12 weeks, resume atezolizumab at fixed

	dose. If not, permanently discontinue atezolizumab.
Grade 3 or 4	• Withhold atezolizumab and cobimetinib. • If event resolves to Grade 1 within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. • If event resolves to Grade 1 within 28 days, resume cobimetinib at fixed dose. If not, permanently discontinue cobimetinib.
Other toxicities not described above	
Grade 3 or 4, or intolerable Grade 2 treatment-related toxicities	• Withhold atezolizumab and cobimetinib. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose level reduced by 1. If not, permanently discontinue cobimetinib.
[a] Resuming atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only	

Table A1.12. Guidelines for managing electrocardiogram QT corrected interval prolonged in response to a*tezolizumab, cobimetinib, and/or hydroxychloroquine*.

Event	Action
QTc > 500ms and change form pre-treatment value remains ≤ 60ms	
1st Occurrence	Temporarily interrupt treatment until QTc decreases below 500 ms; reduce Cobimetinib by 1 dose level
2nd Occurrence	Temporarily interrupt treatment until QTc decreases below 500 ms; reduce Hydroxychlorquine by 1 dose level
3rd Occurrence grade 3	Temporarily interrupt treatment until QTc decreases below 500 ms; reduce Cobimetinib and Hydroxychloroquine by 1 more dose level
Grade 4 Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	Permanently discontinue study drugs
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values	
1st Occurrence	Discontinue drugs permanently

Drugs should be interrupted for 3 ± 2 days and Electrocardiogram repeated until QTc below 500ms for four attempts. Subject should be referred to an electro cardiologist if QTc does not decrease below 500ms after study drug held for greater than 7 days (consecutively).

Table A1.13. Guidelines for managing rhabdomyolysis or CPK elevation in response to a*tezolizumab, cobimetinib, and/or hydroxychloroquine*.

Event	Action
Rhabdomyolysis or CPK elevation	
General guidance	• Evaluate for cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
Asymptomatic CPK elevation, Grade 1, 2, or 3	• Continue study drugs. • Recheck CPK at least once a week.
Asymptomatic CPK elevation, Grade 4	• Withhold cobimetinib, hydroxychloroquine, and if applicable atezolizumab. • If event resolves to Grade ≤ 3 within 28 days, resume cobimetinib and hydroxychloroquine with dose reduced by one level for cobimetinib. If not, permanently discontinue cobimetinib. • Resumption of atezolizumab may be considered in patients who are deriving benefit after discussion with the Principal Investigator.
Rhabdomyolysis or symptomatic CPK elevation	• Withhold all study drugs. • If event improves by at least one grade and symptoms resolve within 28 days, resume cobimetinib and hydroxychloroquine with dose reduced by one level, if possible. If not, permanently discontinue cobimetinib. • Resumption of atezolizumab may be considered in patients who are deriving benefit after discussion with the Principal Investigator.

Table A1.14. Guidelines for managing Immune-related Myocarditis in response to a*tezolizumab, cobimetinib, and/or hydroxychloroquine*.

Event	Action
Myocarditis Events	
Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset and contact Principal Investigator • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider 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, in consultation with Principal Investigator. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab Principal Investigator.
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Principal Investigator. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • 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, in consultation with Principal Investigator. • If event does not improve within 48 hours after initiating corticosteroids, consider adding

	an immunosuppressive agent in consultation with Principal Investigator. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.	

Table A1.15. Guidelines for managing Immune-related nephrotoxicity in response to a*tezolizumab, cobimetinib, and/or hydroxychloroquine*.

Event	Action
Myocarditis Events	
Grade 1	• Continue atezolizumab, cobimetinib, and hydroxychloroquine • Continue atezolizumab, cobimetinib, and hydroxychloroquine
Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset and contact Principal Investigator when considering reinitiation • Refer patient to nephrologist • Initiate treatment with corticosteroids equivalent to 1-2mg/kg/day oral prednisone in consultation with Principal Investigator. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab Principal Investigator.
Grade 3-4	• Permanently discontinue atezolizumab and contact Principal Investigator. • Refer patient to nephrologist and consider renal biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement, in consultation with Principal Investigator. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent in consultation

	with Principal Investigator. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

21.2 Appendix 2: Strong CYP3A4 Inducers and Inhibitors

Table A2.1. Strong CYP3A4 Inducers and Inhibitors.

Strong Inhibitors	Strong Inducers
Protease inhibitors -Ritonavir -Indinavir -Nelfinavir	Anticonvulsants, mood stabilizers -Phenytoin -Carbamazepine -Oxcarbazepine
Macrolide antibiotics -Erythromycin -Telithromycin -Clarithromycin	Non-nucleoside reverse transcriptase inhibitors -Efavirenz -Nevirapine -Etravirine
Azole antifungals -Fluconazole -Ketoconazole -Itraconazole	Phenobarbitol (barbiturate)
Chloramphenicol (antibiotic)	Rifampicin (bactericidal)
Nefazodone (antidepressant)	Modafinil (stimulant)
Bergamottin (constituent of grapefruit juice)	Hyperforin (constituent of St. Johns Wort)
Aprepitant (antiemetic)	Cyproterone (antiandrogen, progestin)
Verapamil (calcium channel blocker)	