COLUMBIA UNIVERSITY MEDICAL CENTER

HERBERT IRVING COMPREHENSIVE CANCER CENTER PROTOCOL

NCI·CC

A Cancer Center Designated by the National Cancer Institute

NCT03979066

TITLE: NEOiPANC - A Phase 2 , Open-Label, Multicenter, Randomized Study Evaluating NEOadjuvant immunotherapy Based Combinations in Patients with Resectable PANCreatic Ductal Adenocarcinoma

Principal Investigator: Gulam Manji, MD, PhD

CUMC IRB#: AAAS1908

TITLE: **NEOiPANC** - A Phase 2 , Open-Label, Multicenter, Randomized Study Evaluating **NEO**adjuvant **immunotherapy** Based Combinations in Patients with Resectable **PANC**reatic Ductal Adenocarcinoma

Coordinating Center: Columbia University Medical Center

Principal Investigator:
Gulam Abbas Manji, M.D./Ph.D.
161 Fort Washington Avenue
New York, NY 10032
Telephone: 212-305-0592
Email address: gam2140@cumc.columbia.edu

Surgeons:
John A. Chabot, M.D.
Columbia University
161 Fort Washington Avenue
New York, NY 10032
Telephone: (212) 305-9468
Email address: jac4@cumc.columbia.edu

Radiologist
Columbia University
Primary: Elizabeth Hecht, M.D.
Secondary: Firas Ahmed, M.D.

Statistician:
Shing M Lee, Ph.D.
722 West 168th Street,
6th Floor, Room 645
New York, NY 10032
Telephone: 212-342-1266
Email address: sml2114@columbia.edu

Regulatory Sponsor:	Gulam Abbas Manji, M.D./Ph.D. 161 Fort Washington Avenue New York, NY 10032 Telephone: 212-305-0592 Email address: gam2140@cumc.columbia.edu
Funding Source:	Genentech/F. Hoffmann-La Roche Ltd.
Study Agent:	Atezolizumab (RO5541267) PEGPH20
Other Agent:	N/A
IND Status:	
F. Hoffmann-La Roche Ltd. Study Number	ML40000

Affiliate Institutions:

Site Principal Investigator and Contact Information:
Memorial Sloan Kettering Cancer Center **Principal Investigator:** **Eileen M. O'Reilly, M.D.** 300 East 66th Street New York, NY 10065 Email: oreillye@mskcc.org **Surgeon:** Vinod P. Balachandran, M.D. **Radiologist:** Primary: TBD Secondary: TBD

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 Declaration of Helsinki, 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 patient. 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 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.

Signature of Principal Investigator Date

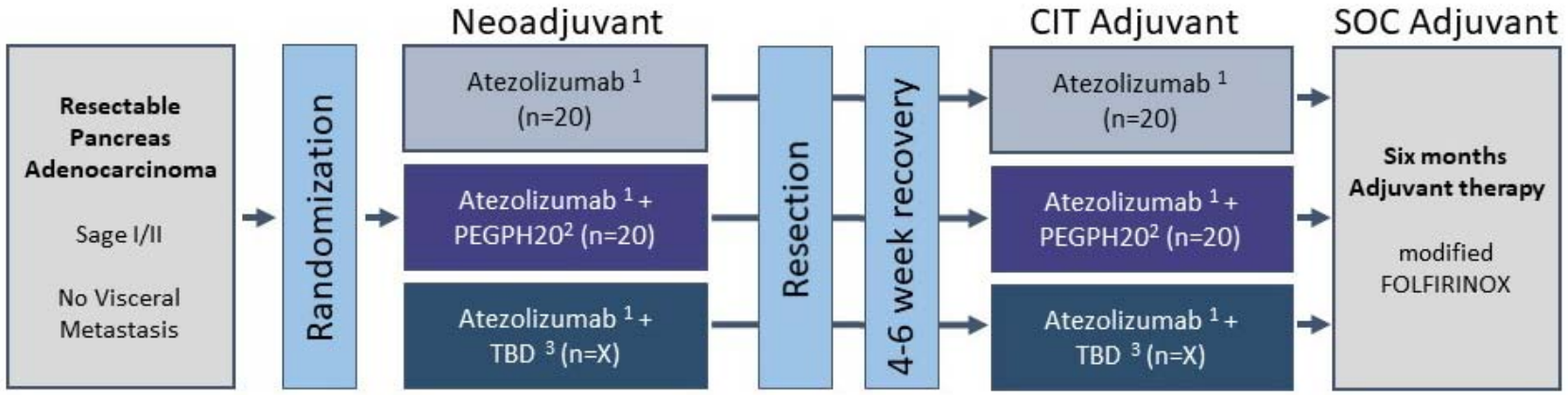
Principal Investigator Name (Print)

Name of Institution

Protocol Synopsis

Title	**NEOiPANC** - A Phase 2 , Open-Label, Multicenter, Randomized Study Evaluating **NEO**adjuvant **immunotherapy** Based Combinations in Patients with Resectable **PANC**reatic Ductal Adenocarcinoma
Short Title	Neoadjuvant atezolizumab based combinations in resectable pancreas cancer
Protocol Number	AAAS1908
Phase	Phase 2
Methodology	Randomized Phase 2 trial for a total of 20 patients per cohort
Study Duration	36–40 months
Study Center(s)	Multicenter; Columbia University Medical Center, and Memorial Sloan Kettering Cancer Center
Objectives	To compare the number of CD8+ T-cells within the tumor with neoadjuvant atezolizumab alone or in combination with PEGPH20 or other therapies (TBD) at time of surgery. To estimate the 18-month recurrence free survival rate and overall survival in each arm.
Number of Patients	Approximately 20 patients are planned for enrollment per cohort.
Diagnosis and Main Inclusion Criteria	Resectable pancreatic adenocarcinoma
Study Product, Dose, Route, Regimen	Cohort 1: Atezolizumab 840mg IV every 2 weeks for 2 doses prior to surgery and 4 doses after surgery. Cohort 2: Atezolizumab 840mg IV every 2 weeks for 2 doses prior to surgery and 4 doses after surgery in combination with PEGPH20 3μg/kg IV twice weekly for 3 weeks prior to surgery and once weekly for 3 weeks (of 28 day cycle) for two cycles after surgery. (Additional cohorts to be added TBD)
Duration of administration	3 weeks prior and 8 weeks after surgery with study drugs 6 months with adjuvant chemotherapy
Reference therapy	Atezolizumab therapy and historical matched controls who did not receive therapy
Statistical Methodology	Primary endpoint is change in number of intratumoral $CD8^+$ T-cells at time of surgery between treatment arm(s) compared to the atezolizumab arm. Group sample sizes of 17 achieve at least 80% power to detect a difference of 1 SD with a significance level (alpha) of 0.05 using a two-sided two-sample t-test.

Protocol Schema



CIT = Cancer Immunotherapy; SOC = standard of care; TBD = to be determined.

[1] Atezolizumab 840 mg IV Days 4 and 18 (neoadjuvant x 2 doses), then x 4 doses (CIT adjuvant) of 28-day cycle;

[2] PEGPH20 3 μg/kg IV Days 1 and 4, weekly, for 3 weeks prior to surgery and weekly on Days 1, 8, and 15 of every 28 days for 2 cycles;

[3] TBD - Other molecules under discussion to be determined.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse events
AESI	adverse events of special interest
CHO	Chinese hamster ovary
CI	confidence interval
CPDM	Clinical Protocol & Data Management
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CUMC	Columbia University Medical Center
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group
EUS	endoscopic ultrasound
ESMO	European Society for Medical Oncology
ESPAC	European Study Group for Pancreatic Cancer
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GA	Gemcitabine and Nab-Paclitaxel
GCP	Good Clinical Practice
HA	hyalouronidase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HICCC	Herbert Irving Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Council for Harmonisation

IEC	independent ethics committee
IF	immunofluorescence
Ig	immunoglobulin
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
LCM	laser capture microdissection
MDCT	multiphasic CT (scan)
MedDRA	Medical Dictionary for Regulatory Activities
MMR-D	mismatch repair-deficient
MMR-P	mismatch repair-proficient
MRI	magnetic resonance imaging
MSE	musculoskeletal events
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OCT	optimum cutting temperature
OS	overall survival
PD-1	programmed death-1
PD	progressive disease
PDA	pancreas adenocarcinoma
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PHI	protected health information
PI	principal investigator
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
qmIF	quantitative multiplex immunofluorescence
RECIST	(immune-modified) Response Evaluation Criteria in Solid Tumors
RFS	recurrence-free survival
SAE	serious adverse event

TAM	tumor-associated macrophages
TC	tumor cells
TE	thromboembolic
TGI	tumor growth inhibition
TIL	tumor-infiltrating lymphocytes
TME	tumor microenvironment
TNF-α	tumor necrosis factor α
ULN	upper limit of normal
UP	unanticipated problem
WHO	World Health Organization

1. INTRODUCTION

Pancreas adenocarcinoma (PDA) is an aggressive cancer for which little progress has been made over the past decades with 5-year survival at 7%, and is projected to be the second leading cause of cancer-related death in the United States in 2030 (Rahib et al. 2014; Siegel et al. 2016). Even for early stage disease, recurrence is high. Although recent combination therapies for metastatic PDA have improved survival by up to 5 months, the overall prognosis remains little changed and novel therapies are desperately needed (Conroy et al. 2011; Von Hoff et al. 2013). The majority of patients diagnosed with PDA either have locally advanced (~ 30%) or distant (~ 50%) disease, for which chemotherapy is the mainstay of treatment (Howlader et al. 2017). Of those that receive surgery followed by adjuvant chemotherapy, the median overall survival remains poor (20.1 to 54.4 months) (Neoptolemos et al. 2004; Oettle et al. 2007; Regine et al. 2008; Neoptolemos et al. 2010; Howlader et al. 2017; Conroy et al. 2008). Negative margins, smaller tumor size, and lack of lymph node involvement result in improved prognosis (Allison et al. 1998; Sohn et al. 2000; Howard et al. 2006). Patients with metastasis to visceral organs, peritoneum, or lymph nodes that are beyond the field of resection derive no benefit from surgery.

Of the newly diagnosed patients, nearly 15% are considered to be candidates for immediate surgical resection (Vincent et al. 2011). Despite resection, disease recurs in a majority of these patients and the median disease- free survival is 6.7 months (Oettle et al. 2013). Addition of capecitabine to gemcitabine has improved median overall survival from 25.5 to 28.0 months (HR 0.82, p=0.032) compared to those patients treated with gemcitabine alone (Neoptolemos et al. 2017). However, preliminary experience with use of this regimen in the United States has posed to be a challenge as most patients are unable to tolerate the doses used in the European ESPAC-4 trial and require frequent dose reductions or schedule modifications. PRODIGE 24, a large randomized phase 3 study compared mFOLFIRINOX to gemcitabine monotherapy in the adjuvant setting and demonstrated a median overall survival benefit of 54.4 months compared to 35.0 months, respectively. 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). The reported 18-month overall survival (OS) is 67% with adjuvant gemcitabine in combination with capecitabine which is similar to the 63% reported when gemcitabine and oxaliplatin were tested in the neoadjuvant setting (O'Reilly et al. 2016). Although mFOLFIRINOX yielded impressive results, patients enrolled onto the study had a better performance status to withstand mFOLFIRINOX.

A majority of resectable patients likely have micrometastatic disease at time of diagnosis and therefore benefit from adjuvant chemotherapy. It is in this setting that

immunotherapy either alone or in combination with agents that disrupt the immunosuppressive tumor microenvironment (TME) are likely to be effective in controlling micro metastatic foci of disease. Effective treatments to at least prolong the disease-free duration if not increasing the cure rate, are desperately needed for this fatal disease.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To compare the number of CD8+ T cells within the tumor after neoadjuvant atezolizumab alone or in combination with PEGPH20 or other therapies at time of surgery.

2.2 SECONDARY OBJECTIVE

a) To estimate the 18-month survival rate and overall survival in patients treated with atezolizumab vs atezolizumab + PEGPH20 or other therapies followed by surgery and adjuvant therapy.

b) To determine the R0 resection rates with atezolizumab vs atezolizumab + PEGPH20 or other therapies administered in the neoadjuvant setting.

c) To determine the safety profile with atezolizumab vs atezolizumab + PEGPH20 or other therapies followed by surgery and adjuvant therapy.

d) To evaluate Ca 19-9 biomarker responses to atezolizumab with or without PEGPH20 or other therapies in the neoadjuvant setting.

e) To evaluate patterns of failure following neoadjuvant atezolizumab with or without PEGPH20 or other therapies and surgery.

f) Intratumoral CD8+ T cells after neoadjuvant atezolizumab alone or combination with PEGPH20 or other therapies at time of surgery will be compared to intratumoral CD8+ T cells within resected tumors after no neoadjuvant therapy from matched historical controls.

2.3 EXPLORATORY OBJECTIVE

a) To isolate the epithelium and stromal tumor for protein expression profiling using RNA-seq for subtype classification of PDA. This will be performed using laser-capture microdissection (LCM) on resected tissue samples from patients treated with atezolizumab vs atezolizumab + PEGPH20 or other therapies

b) To quantitate the change in $CD8^+$ T cells within paired pre-treatment biopsy and on-treatment resected tumor treated with atezolizumab vs atezolizumab + PEGPH20 or other therapies.

c) To quantitate distinct immune subtypes within on-treatment resected tumor treated with atezolizumab vs atezolizumab + PEGPH20 or other therapies by quantitative multiplex immunofluorescence.

d) To quantitate the change in immune subtypes within paired pre-treatment biopsy and on-treatment resected tumor treated with atezolizumab vs atezolizumab + PEGPH20 or other therapies.

3. BACKGROUND

Presently, surgical resection offers the only therapeutic means of cure. However only 15%-20% of patients are found to have resectable disease at time of initial diagnosis. Of the patients who undergo curative surgery, most will relapse and eventually succumb to the disease. 5-year survival rates for node-negative and -positive disease at time of pancreatic duodenectomy are 25%-30% and 10%, respectively (Trede et al 1990; Geer and Brennan 1993; Yeo et al. 1995).

3.1 IMMUNOTHERAPY IN PDA

Multiple studies have shown that genetic mutations in tumor DNA can lead to the expression of antigenic peptides which can drive the anti-tumor therapeutic immune response unleashed by immune checkpoint inhibitors (Snyder et al. 2014; Azuma et al 2014; Rizvi et al. 2015). Neoantigen-specific lymphocytes can be detected in peripheral blood samples and their levels correlate with disease response to anti-programmed death-1(PD-1) therapy. PDAs are characterized by a moderate mutational burden (averaging 67 coding mutations) comparable to other solid tumors (Brahmer et al. 2010; Mu et al. 2011; Brahmer et al. 2012). However, early phase monotherapy anti-CTLA-4 and anti-programmed death ligand-1(PD-L1) antibody trials in patients with metastatic and locally advanced PDA demonstrated limited activity (Royal et al. 2010; Brahmer et al. 2012). Interim results of a multicenter, phase 1 trial involving the anti-PD-L1 mAb, durvalumab, were presented at European Society for Medical Oncology (ESMO) and showed a disease control rate of 21% (6 of 29 patients) in PDA patients, two of whom achieved a partial response (Segal et al. 2014). Although PDA has been considered a non-immunogenic cancer, these studies demonstrate that PDA can respond to immunotherapy and that further study is warranted.

A leading explanation for the lack of efficacy of single-agent immunotherapy is the highly immunosuppressive stroma that envelopes most malignant cells. PDAs contain very few effector T cells, and in surgically resected tumors a higher number of tumor-infiltrating lymphocytes (TILs) correlates with improved survival (Fukunaga et al. 2004). Untreated PDAs are characterized by low PD-L1 expression, where only 12% of tumors analyzed expressed membranous staining of PD-L1 in more than 5% of neoplastic cells (Soares et al. 2015). Interestingly, a retrospective study evaluating resected PDA tissue identified that PD-L1 staining inversely correlated with survival and $CD8^+$ T-cell

infiltration (Nomi et al. 2007). This suggests that targeting PD-L1 may unmask at least part of the immunosuppression function within PDA. Furthermore, evaluation of a monoclonal agonist antibody targeting CD40, in combination with gemcitabine, detected four partial responses in 22 patients with advanced PDA while other patients experienced decreased fluorodeoxyglucose (FDG) uptake within their primary and/or metastatic lesions on positron emission tomography (PET)/computed tomography (CT) scans (Beatty et al. 2013). Furthermore, recent reports indicated that immunotherapy appears to be effective in patients with microsatellite high PDA tumors (see below). Collectively, these findings suggest that immunotherapy has a role in PDA.

3.2 MISMATCH REPAIR PATHWAY AND SUSCEPTIBILITY TO IMMUNOTHERAPY

Of particular interest is the observation that patients with mismatch repair-deficient (MMR-D) PDA respond to checkpoint inhibitors (Rizvi et al. 2015). MMR-D colorectal cancer tumors have 10 to 100 times as many somatic mutations compared to mismatch repair-proficient (MMR-P) colorectal tumors (Timmermann et al. 2010). In a phase 2 study that included 10 patients with MMR-D colorectal cancer, four exhibited an immune- related objective response compared to none of the nine within the MMR-P cohort when treated with pembrolizumab monotherapy. At the time the study was published, median progression-free survival and OS was not reached within the MMR-D cohort, while it was 2.2 and 5.0 months, respectively, within the MMR-P cohort (Rizvi et al. 2015; Neoptolemos et al. 2017). Whole-exome sequences identified a mean of 1782 somatic mutations per tumor in patients in nine MMR-D colorectal cancer patients, compared with 73 mutations per tumor in patients with MMR-P. Membranous PD-L1 expression occurred only in tumors of MMR-D patients and was prominent on TILs and tumor-associated macrophages at the invasive fronts of the tumor (Lee et al. 2015). The leading hypothesis to the responsiveness of MMR-D colorectal cancer to PD-1 targeted therapy is the increased number of mutation-associated neoantigens. An additional preliminary report of 4 patients with PDA identified that 2 had partial responses and 2 had stable disease (Rizvi et al. 2015). However, PDA with MMR-P tumors constitute greater than 98% of cases for which immunotherapy is not currently efficacious.

3.3 STUDY RATIONALE

Atezolizumab Arm

Although early phase trials have not offered great success in the metastatic setting for patients with PDA, interim analysis of a multicenter, phase 1 trial with durvalumab presented at ESMO indicated a disease control rate of 21% (Ene-Obong et al. 2013). As mentioned previously, PD-L1 expression correlates with poor prognosis and decreased $CD4^+$ and $CD8^+$ T cell infiltration within the tumor. Targeting PD-L1 in the micrometastatic setting (resectable disease), when robust mature immunosuppressive

pathways may not have yet formed, may be the optimum time to investigate anti-PD-L1 therapy. This arm of the study aims to test if atezolizumab is able to modulate CD8+ T-cell infiltration compared to historical matched controls. As a secondary endpoint we will also evaluate how clinical outcomes compare to matched historical controls.

Atezolizumab + PEGPH20 Arm

Neoplastic, immune, and stromal cells within PDA reside in a highly dense desmoplastic environment composed of an extracellular matrix of which hyalouronidase (HA) is an abundant component. HA is a linear glycosaminoglycan and an integral component of not only PDA tumors, but has also been shown to accumulate in many solid tumors and is associated with a poor prognosis and increased immunosuppression (Provenzano et al. 2012; Cheng et al. 2013). In a preclinical autochthonous mouse model of PDA, Sunil Hingorani s group demonstrated that the interstitial fluid pressures were unusually high within tumors that exhibited a high HA content. Furthermore, high HA tumors contained low vascularity, which compromised delivery of chemotherapeutic agents, such as gemcitabine. Mice treated with hyaluronidase resulted in decreased HA content and microvasculature re-expansion within tumors which led to a survival benefit (Provenzano et al. 2012). These preclinical studies led to early phase clinical studies in metastatic PDA where addition of PEGPH20 to gemcitabine and nab-paclitaxel (GA) in a randomized phase 2 study demonstrated a survival benefit in patients with HA-high tumors. The objective response rate for patients who were treated with a combination of PEGPH20 and GA compared to GA alone was 45% versus 31%, respectively, and the median overall survival was 11.5 versus 8.5 months, respectively (hazard ratio (HR), 0.96; 95% CI, 0.57 to 1.61) (Hingorani et al. 2018). A large phase 3 randomized clinical trial in the high HA stage IV PDA population in the first line setting is ongoing.

PDA likely invokes multiple immune evading mechanisms which result in its aggressive behavior; it is expected that multiple agents will likely be needed to develop effective therapies. One such rationale is the combination of PEGPH20 and immune checkpoint blockade to allow increased cytotoxic T-cell infiltration by increasing vascular permeability and decreasing interstitial pressure. In a breast cancer preclinical model, PEGPH20 resulted in an increase accumulation of $CD8^+$ TIL by 176% (p=0.0025) and improved tumor growth inhibition by 38% relative to anti-PD-L1 alone (86% vs 62.4%, p=0.0024) (Clift et al. 2017). Other preclinical studies are also demonstrating increased $CD8^+$ T-cell infiltration with addition of PEGPH20 and improved tumor control in combination with immune checkpoint blockade (Lee et al. 2017). These and other preclinical studies suggest that this combination is worth pursuing in patients with resectable PDA. The combination is hoped to increase $CD8^+$ T-cell infiltration within the primary tumor for improved immune mediated cytotoxicity and decreased interstitial pressure to allow improved surgical resections. Hypothetically, the combination should also be effective in foci of micrometastasis, where the TME may not be as mature.

Identified risks for PEGPH20 include musculoskeletal events (MSEs), infusion-related reactions (IRRs), and thromboembolic (TE) events.

4. INVESTIGATIONAL AGENT

4.1 ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody which targets PD-L1 on tumor-infiltrating immune cells or tumor 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 by 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.

4.1.1 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.

4.1.2 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 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. For safety of atezolizumab in humans, please refer to Section 11.1.

4.2 OTHER AGENTS

PEGPH20

PEGPH20 is a PEGylated, neutral-pH-active human hyaluronidase PH20 produced by recombinant DNA technology. PEGPH20 drug product is supplied as an aqueous solution containing 0.330 mg/mL PEGPH20 with 10 mM succinic acid, 130 mM NaCl and 10 mM L-methionine at pH 6.2. Each vial contains 1.2 mL (0.36 mg, current investigational material) or 1 mL (0.303 mg, commercial-scale material) of PEGPH20 drug product. PEGPH20 has a terminal plasma half-life of approximately 3.2 hours in rodents and 50 hours in monkeys. In humans, data from 2 patients treated with 50 g/kg PEGPH20 in Study HALO-109-101 demonstrated a plasma half-life of 2.5 to 4.8 hours for the initial phase and 26 to 49 hours (1-2 days) for the terminal phase. In this study, atezolizumab will be given 1−3 hours after completion of PEGPH20 administration on days where PEGPH20 and atezolizumab are administered the same day.

Oxaliplatin

Oxaliplatin is a platinum-based antineoplastic agent. It inhibits synthesis of deoxyribonucleic acid (DNA) by cross-linking guanine and cytosine. Please refer to local prescribing information for detailed instructions on the reconstitution, storage conditions, intravenous (IV) administration, known precautions, and warnings of oxaliplatin.

Irinotecan

Irinotecan is an antineoplastic agent which is activated by hydrolysis to SN-38, an inhibitor of topoisomerase I. SN-38 is subsequently inactivated by glucouronidation by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). The inhibition of topoisomerase by SN-38 results in inhibition of DNA replication and transcription to RNA synthesis. Please refer to local prescribing information for detailed instructions on the

reconstitution, storage conditions, intravenous (IV) administration, known precautions, and warnings of irinotecan.

Leucovorin

Leucovorin, also known as folinic acid, is a derivative of tetrahydrofolate and is used in combination with fluorouracil to enhance the effect of fluorouracil metabolite by stabilizing the bond with thymidylate synthetase. Please refer to local prescribing information for detailed instructions on the reconstitution, storage conditions, intravenous (IV) administration, known precautions, and warnings of leucovorin.

Fluorouracil

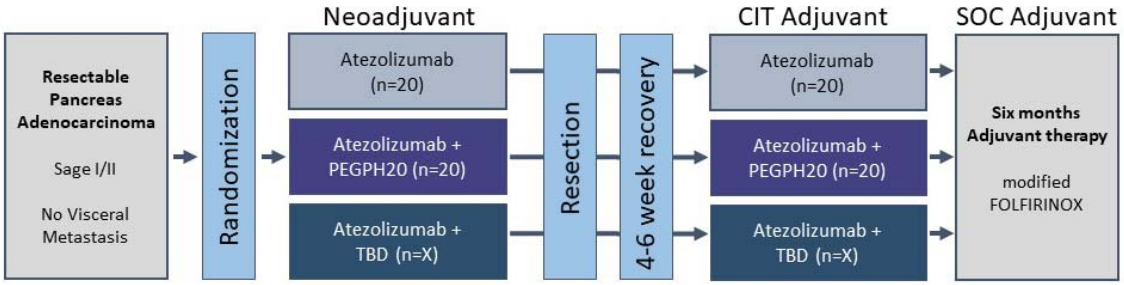
Fluorouracil is an antineoplastic agent which functions by multiple mechanism but primarily by inhibiting thymidylate synthase (TS) which is required for formation of thymidine. Fluorouracil results in decline of thymidine monophosphate, an essential nucleoside resulting in the death of rapidly dividing neoplastic cells. Please refer to local prescribing information for detailed instructions on the reconstitution, storage conditions, intravenous (IV) administration, known precautions, and warnings of fluorouracil.

5. STUDY DESIGN

5.1 GENERAL DESIGN

Newly diagnosed resectable PDA patients who meet the study criteria will be randomly assigned to one of the treatment arms (Figure 1**Error! Reference source not found.**).

Figure 1 Overall Study Design

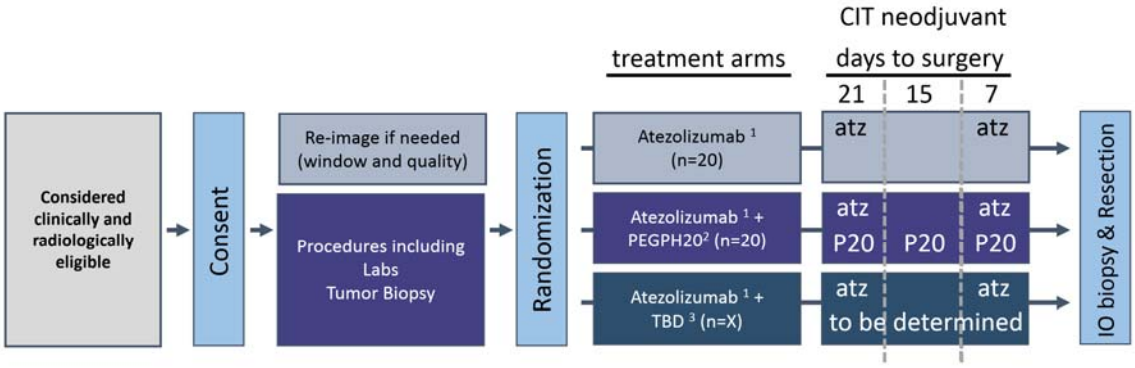


CIT = cancer immunotherapy; SOC = standard of care; TBD = to be determined.

Patients with tumors that are deemed resectable will be randomly assigned to receive either atezolizumab alone, or atezolizumab in combination with PEGPH20 or other therapies for a period of 3 weeks prior to undergoing surgical resection. Patients will recover for 4 to 6 weeks and then continue on the same treatment for an additional 8 weeks, after which they will receive adjuvant modified FOLFIRINOX for 6 months.

Subjects deemed eligible will undergo CT of the chest, and triple-phase CT of the abdomen and pelvis using the pancreas protocol (14-day window prior to treatment) and consent for the study if considered to have resectable disease and meet the eligibility criteria. All eligibility criteria will be reviewed during the consent process and all study related procedures will be performed after consenting. A fresh pancreas tumor biopsy is required prior to initiating therapy. Patient will recover for at least 2 days after biopsy to initiate therapy for 3 weeks. Atezolizumab will be administered at 840 mg IV every 2 weeks (for 2 doses total) prior to surgery (Days 4 and 18). PEGPH20 will be administered at 3 μg/kg on Days 1 and 4 every 7 days for 21 days. Figure 2 depicts required assessments prior to surgery. Patients receiving PEGPH20 will receive enoxaparin to mitigate the increased risk of thromboembolism to start on Cycle 1, Day 1 and discontinue 2 days prior to scheduled surgery and resume 2-7 days after surgery if deemed appropriate. Patients will continue enoxaparin for 7 days after last dose of PEGPH20.

Figure 2 Study Design for Neoadjuvant Therapy



atz = atezolizumab; CIT = Cancer Immunotherapy; IO = intraoperative; P20 = PEGPH20; TBD = to be determined.

After meeting eligibility criteria, patients will consent for the study and will undergo schedule of activities including repeat imaging (if needed) and tumor biopsy prior to being randomized to distinct treatment arms. Treatment should be initiated no later than 5 days after randomization. Patients will be treated either with atezolizumab alone or in combination with PEGPH20 or other agent for 21 days prior to intraoperative (IO) biopsy and surgical resection.

[1] Atezolizumab 840 mg IV Day 4 and 15 (neoadjuvant x 2 doses; 1 week break prior to resection), then x 4 doses (CIT adjuvant) every 2 weeks.

[2] PEGPH20 will be administered at 3 μg/kg on Day 1 and Day 4 every seven days for 21 days

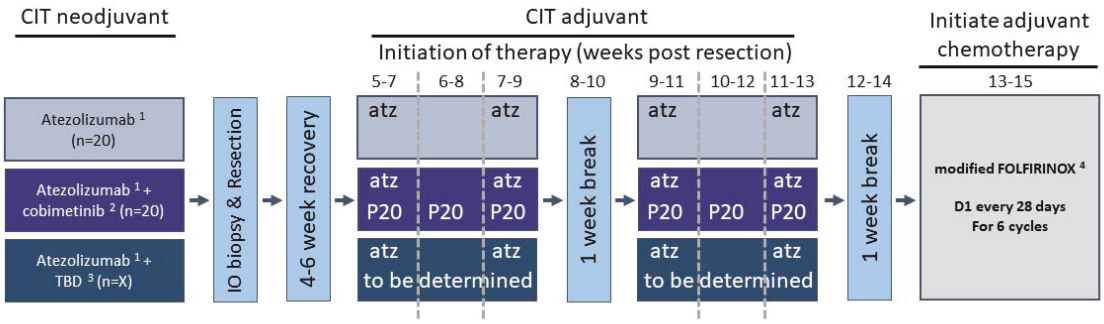
[3] Other molecules under discussion.

The preoperative biopsy, intraoperative biopsy, and the resected tumor sample will be analyzed for $CD8^+$ T-cell infiltration, other immune cells of interest, and undergo RNA expression analysis of the epithelial and stromal component by laser capture microdissection as described in Section 7.

A safety committee of participating surgeons and medical oncologists at Columbia University Medical Center (CUMC), Memorial Sloan Kettering Cancer Center (MSKCC), and other participating sites will convene on a regularly scheduled basis to discuss study conduct. ***If greater than 1 of the 20 patients per cohort are unable to undergo surgery, or greater than 3 of the 20 patients per cohort have a greater than 14-day delay in surgery, deemed related to study treatment, enrollment to that arm will be halted and an analysis performed by the Principal Investigator (PI). The Institutional Review Board (IRB) and the Data Safety Monitoring Committee (DSMC) will be notified within 14 days after every occurrence when a subject has surgery delayed by greater than 14 days or when the subject is considered not to be a surgical candidate deemed related to study treatment.***The PI, in consultation with the safety committee, will either modify the treatment regimen or discontinue the arm if an alternate safe regimen is not deemed feasible. After a recovery period of 4-6 weeks post-surgical resection, patients will resume the same treatment which they received prior to surgery for an additional 8 weeks (2 cycles). At the end of investigational therapy, patients will initiate adjuvant chemotherapy with modified FOLFIRINOX for 6 cycles. Patients will be followed for recurrence and survival.

All study-related investigational treatment should end at or prior to Week 14, Day 6 after surgery. Adjuvant chemotherapy should begin no later than Week 16, Day 1 after surgery even if partial treatment is administered within a treatment cycle. All study-related therapy should be discontinued at least 1 week prior to initiation of chemotherapy (**Error! Reference source not found.**). Doses being held due to safety concerns will resume dosing at the previous schedule when treatment is deemed safe. Oral agents that are vomited or missed by the patient will not be made up.

Figure 3 Study Design for Adjuvant Therapy



atz = atezolizumab; CIT = Cancer Immunotherapy; D = Day; IO = intraoperative; P20 = PEGPH20; TBD = to be determined.

After completing neoadjuvant immunotherapy, intraoperative (IO) biopsy and surgical resection, patients will recover for 4 to 6 weeks after surgery. Patients will be treated with 2 cycles of either atezolizumab alone (Days 1 and 15, every 28 days) or in combination with PEGPH20 (P20; Days 1, 8, and 15, every 28 days) starting Week 5 or 7, Day 1, weekly with PEGPH20 (depending on duration of post-surgical recovery) and will undergo 2 cycles of therapy. Adjuvant chemotherapy will begin between Weeks 13 and 16, Day 1 (depending on duration of post-surgical recovery) for 6 months.

1 Atezolizumab will be administered 840 mg IV on Days 1 and 15, every 28 days for 2 cycles.
2 PEGPH20 will be administered 3 μg/kg on Days 1, 8, and 15, every 28 days for 2 cycles.
3 Other molecules under discussion.
4 modified FOLFIRINOX Oxaliplatin 85mg per square meter IV, irinotecan 150mg per square meter IV, leucovorin 400mg per square meter IV, and fluorouracil 2400mg per square meter IV continuous infusion on day 1 and pegfilgastrim 6mg SC injector kit on day 3 every 2 weeks.

5.2 NUMBER OF PATIENTS

Arm A: Atezolizumab (n=20)

Arm B: Atezolizumab + PEGPH20 (n=20)

6. PATIENT SELECTION AND WITHDRAWAL

6.1 INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

6.1.1 Histological or pathological confirmation of pancreatic adenocarcinoma

Cytologic or histologic proof of PDA needs to be verified by the treating institution pathologist either from the initial diagnostic biopsy, or from the required pre-treatment biopsy and prior to initiation of any study-related therapy

6.1.2 Extent of disease.

Stage 1 or 2 PDA (See Section 6.3 for radiological criteria and Appendix 1) and patient deemed a surgical candidate by the PI in consultation with the designated site radiologist and surgeon at the treating institution

6.1.3 No prior surgical, systemic or radiotherapy for PDA.

6.1.4 ECOG performance status of 0 or 1.

6.1.5 Age $\geq$ 18 years.

6.1.6 Adequate hematological and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:

- ANC ≥ 1.5×10^9/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 within 4 weeks.
- Hemoglobin (Hgb) >9.0 g/dL without transfusion within 2 weeks.
- AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × upper limit of normal (ULN) unless elevated secondary to biliary obstruction from the pancreas mass and amenable to decompression prior to initiation of therapy. Prior to initiation of therapy, AST, ALT, and ALP ≤ 2.5 × ULN.
- Serum total bilirubin ≤ 1.5 × ULN unless in patients with known Gilbert disease (≤ 3 × ULN) or unless elevated secondary to biliary obstruction from the pancreas mass and amenable to decompression prior to administration of investigational therapy. A functioning biliary stent as evidenced by declining total bilirubin and ≤ 2 × ULN is required prior to initiation of therapy.
- Albumin ≥ 3.0 g/dL.
- Creatinine within ULN or calculated creatinine clearance (CrCl) >50 mL/min using the Cockcroft-Gault formula.
- INR and aPTT ≤ 1.5 × ULN.

6.1.7 Tumor accessible for fresh biopsy

6.1.8 Women of child-bearing potential must have a negative serum pregnancy test at screening and must agree to use two forms of effective contraception from the time of the negative pregnancy test and for a minimum of 5 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 will be considered not of child-bearing potential if amenorrheic at least for one year or have undergone surgical sterilization.

6.1.9 Fertile men must agree to use an effective method of birth control during the study and for up to 5 months after the last dose of study drug.

6.1.10 Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

6.1.11 Able to comply with the study protocol, in the investigator s judgment.

6.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from study entry:

Exclusion Criteria Related to Medications

6.2.1 Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, including but not limited to anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies.

6.2.2 Patients who are receiving any other investigational agents concurrently.

6.2.3 Concomitant treatment with other anti-neoplastic agents (hormonal therapy acceptable).

General Medical Exclusions

6.2.4 Uncontrolled pleural effusion, pericardial effusion, or ascites.

6.2.5 Patient receiving therapeutic doses of anticoagulation.

6.2.6 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.

6.2.7 Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sj gren s syndrome, Guillain-Barr syndrome, or multiple sclerosis, with the following exceptions:

- Patients with a history of autoimmune-related hypothyroidism who are on 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.

6.2.8 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 CT scan

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

6.2.9 Positive HIV test at screening or at any time prior to screening.

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

6.2.10 Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening.

Note: 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.

6.2.11 Active hepatitis C virus (HCV) infection, defined as having a 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.

6.2.12 Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease, and inherited liver disease.

6.2.13 Known active tuberculosis.

6.2.14 Severe infection within 4 weeks prior to initiation of study treatment, including, but 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 $\leq 2 \times$ 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.

6.2.15 Treatment with therapeutic oral or 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.

6.2.16 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.

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

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

6.2.19 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. Patients with history of prior malignancies should have risk of recurrence within 3 years after screening to be less than 90% (to be discussed with the PI for final determination of eligibility).

6.2.20 Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with atezolizumab or within 5 months after the last dose of atezolizumab.

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

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

6.2.23 Known allergy or hypersensitivity to any of the study drugs or any of their excipients.

6.2.24 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment.

6.2.25 Treatment 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 anticipation of 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 less than 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 PI has been obtained.

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

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

6.2.28 Major surgical procedure or significant traumatic injury within 14 days of initiating study.

6.2.29 Previous radiotherapy to 25% or more of the bone marrow.

6.2.30 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.

6.2.31 Considered ineligible to receive full standard dose modified FOLFIRINOX therapy in the adjuvant setting.

6.2.32 Peripheral neuropathy > Grade 1

6.2.33 History of allergy or hypersensitivity to oxaliplatin, irinotecan, leucovorin, fluorouracil, pegfilgastrim, or any excipients.

6.2.34 History of Gilbert s disease or known genotype UGT1A1 *28/*28.6.2.35 Inflammatory disease of the colon or rectum, or severe uncontrolled diarrhea.

Exclusion Criteria for PEGPH20-Containing Arm

Patients who meet any of the following criteria will be excluded from the PEGPH20-containing arm:

6.2.35 Risk of thromboembolic events which are defined as:

- History of transient ischemic attack requiring intervention or treatment, carotid artery disease requiring interventions or treatment, of cerebrovascular accident
- Evidence of deep vein thrombosis (DVT), pulmonary embolism, or other thromboembolic event at screening, except

  - Superficial vein thrombosis
  - Visceral or splanchnic vein thrombosis if the thrombosis is at a location near the site of underlying PDAC which may contribute to the etiology of the thrombus
- Treatment with megestrol acetate within 14 days prior to initiation of study treatment

6.2.36 Unable to use low-molecular-weight heparin

Criteria to initiate chemotherapy

1. Full recovery from surgery and subject able to receive chemotherapy.
2. Subjects who have evidence of recurrent disease prior to initiation of chemotherapy will need to undergo biopsy to prove disease recurrence if deemed safe.
3. Hematological
   a. ANC ≥ 1.5×10^9 /L without granulocyte colony-stimulating factor support.
   b. Platelet count ≥100×10^9 /L (100,000/μL) without transfusion within 4 weeks.
   c. Hemoglobin (Hgb) >9.0 g/dL
   d. AST, ALT, and alkaline phosphatase (ALP) ≤ $2.5 \times$ upper limit of normal (ULN)
   e. Albumin ≥ 3.0 g/dL.
   f. Creatinine within ULN or calculated creatinine clearance (CrCl) >50 mL/min using the Cockcroft-Gault formula.

6.3 RADIOLOGICAL DEFINITION FOR RESECTABLE

Disease Criteria for Resectable Disease

Radiographic reading must be consistent with resectable cancer of the pancreas as defined by National Comprehensive Cancer Network (NCCN) guidelines and must meet the following criteria on CT/magnetic resonance imaging (MRI):

1. No tumor metastasis in the chest, abdomen, or pelvis.
2. No arterial involvement:
   - No tumor contact (solid or hazy soft tissue) with aorta.
   - No tumor contact (solid or hazy soft tissue) with celiac axis.
   - No tumor contact (solid or hazy soft tissue) with superior mesenteric artery.
   - No tumor contact (solid or hazy soft tissue) with common hepatic artery.
3. No ″inoperable″ venous involvement

None or <180 degrees tumor contact with the superior mesenteric vein (without vein contour irregularity or thrombosis,

   -).
   - None or <180 degrees tumor contact with portal vein (without vein contour irregularity or thrombosis).

Patients with pancreatic tumor extending to the above organs or with metastasis will be considered borderline resectable or non-resectable and thus should be excluded from the study.

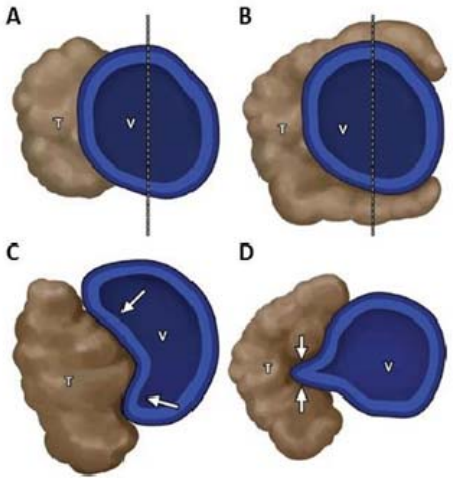


Figure 4 Venous Tumor Contact

A. Less than or equal to 180^{O} tumor contact without deformity. **B.** Greater than 180^{O} tumor contact without deformity. **C.** Less than or equal to 180^{O} contact with deformity (arrows). **D.** Tear drop deformity (arrows). *T:*tumor, *V:*vein. Dashed line: 180^{O} of lumen circumference. Figure adapted from Al-Hawary et. al. 2014.

Table 1 Radiographic Image Assessment - Baseline Review within Seven Days of Initiating Therapy

CT/MRI RESULTS

Was a CT or MRI of the abdomen performed? ☐Yes ☐No

(If yes), Date of CT or MRI of abdomen *(mm/day/yyyy)* _____

(If yes), Primary tumor identified ☐Yes ☐No ☐Not evaluable

(If yes), Location of tumor ☐Head/Neck/Uncinate ☐Body/Tail

(If yes), primary tumor size

Dimension 1_____*(mm*) Dimension 2_____*(mm*)

CRITERIA FOR RESECTABLE DISEASE

- Tumor contact with aorta ☐Yes ☐No
- Tumor contact with celiac axis ☐Yes ☐No
- Tumor contact with superior mesenteric artery ☐Yes ☐No
- Tumor contact with common hepatic artery ☐Yes ☐No
- Tumor contact with superior mesenteric vein ☐Yes ☐No
  - If yes →
    - tumor involvement >180 degrees ☐Yes ☐No
    - SMV contour irregularity or thrombosis ☐Yes ☐No
- Tumor contact with portal vein ☐Yes ☐No
  - If yes →
    - tumor involvement >180 degrees ☐Yes ☐No
    - If yes → PV contour irregularity or thrombosis ☐Yes ☐No
- Tumor metastasis in chest, abdomen, or pelvis ☐Yes ☐No

RADIOGRAPHIC STAGE

Radiographic stage *(check one)*

☐**Resectable**
☐Non-resectable
☐Metastatic
☐Not evaluable

6.4 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

Table 2 Accrual Targets for Women and Minority

Accrual Targets					
	Sex/Gender				
Ethnic Category	**Females**		**Males**		**Total**
Hispanic or Latino	4	+	4	=	8
Not Hispanic or Latino	16	+	16	=	32
Ethnic Category: Total of All Patients	20	+	20	=	40
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	2	+	2	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	18	+	18	=	36
Racial Category: Total of All Patients	20	+	20	=	40
	(A1 = A2)		(B1 = B2)		(C1 = C2)

6.5 PATIENT RECRUITMENT

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

6.6 EARLY WITHDRAWAL OF PATIENTS

6.6.1 When and How to Withdraw Patients

- If at any time the patient develops confirmed disease recurrence, he/she will be taken off study and referred for alternative therapy. For guidance on treatment beyond recurrence please refer to Section 13.2. All patients who received any investigational therapy will be followed for survival.
- Where possible, a biopsy will be required to confirm disease recurrence and the determination of disease recurrence will not be adjudicated on imaging or Ca 19-9 levels alone.

- If at any time the patient develops unacceptable toxicity, he/she will be removed from study.
- If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Patient Eligibility (i.e., 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.
- If the patient withdraws consent for continued participation, he/she will be removed from study.
- The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse event, clinically significant disease recurrence, patient request, investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor or institutional review board (IRB)/independent ethics committee (IEC). When a patient discontinues or is withdrawn, the investigator will notify the Sponsor and should perform the procedures indicated in the End of Study column in the Schedule of Events within 28 days after discontinuation of study drug and before initiation of any new anti-cancer therapy. Follow-up information will be obtained for patients who discontinue their participation in or are withdrawn from the study.
- Patients withdrawn from the study for reasons other than toxicity or clinically significant disease recurrence (e.g., protocol violation or noncompliance) will be replaced. Study drug administration may be discontinued for an adverse event or at the discretion of the investigator.

6.6.2 Data Collection and Follow-up for Withdrawn Patients

- If a patient withdraws consent to participate in the study, every attempt will be made to follow all patients for survival.

7. TISSUE CORRELATION

Sample processing for $CD8^+$ T-cell quantification

We believe that the combinations being tested, including atezolizumab combined with PEGPH20, compared to atezolizumab alone, will result in an increase in CD8+ T-cell infiltration within the tumor microenvironment.

A detailed protocol of tissue processing is provided in the laboratory manual. Briefly, required endoscopic ultrasound-guided pre-treatment biopsy will be performed to obtain at least four additional tumor cores if deemed safe. Required on-treatment repeat biopsy to obtain at least four research tumor cores will be performed under direct visualization of the pancreas tumor by the operating surgeon at time of surgical resection within the operating room immediately preceding excision of the tumor if deemed safe. Alternatively, if deemed unsafe or concern for tumor seeding the resection bed or

contamination of tumor tissue with gastric contents, resected tumor will undergo core biopsies immediately post resection within the operating room. Tissue samples are to be sent to the address 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 allow for shipment delays which would ensure timely delivery of bio-specimens.

Sample processing of RNA-Seq expression

A detailed protocol of tissue processing is provided in the laboratory manual. Briefly, fresh frozen tissue will be obtained from endoscopic ultrasound (EUS)-guided biopsy and surgically resected tissue and immediately sectioned and microscopically evaluated. Suitable samples will be transferred into optimum cutting temperature (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. Frozen blocks will be sent to Dr. Manji s laboratory for further processing as per established protocol. Tissue samples are to be sent to the address 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 allow for shipment delays which would 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: 212-851-4507
Alternate: 518-488-4704

7.1 TRANSLATIONAL SCIENCE

7.1.1 PDA Subtypes as Defined by Immune Cell Infiltrate and Gene Expression

CD8+ T-Cell Infiltration and PDA Survival

$CD8^+$ TILs, which are known anti-tumor effector cells, are rarely found in the PDA tumor microenvironment (Vonderheide and Bayne 2013). This may in part be explained by the unique desmoplastic stroma, found adjacent to PDA tumor cells, which may act as a physical barrier to T-cell infiltration although this hypothesis has been challenged by a recently reported study (Ene-Obong et al. 2013; Carstens et al. 2017). In addition, the PDA stroma is typically infiltrated with significant numbers of immunosuppressive leukocytes including tumor-associated macrophages, myeloid-derived suppressor cells (MDSC), and regulatory T cells (Hiraoka et al. 2006; Clark et al. 2007). Nevertheless, 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 et al. 2013; Deng et al. 2016). Human pancreas tumor probed for distinct markers using quantitative multiplex immunofluorescence (qmIF) which identifies specific immune subtypes is depicted in

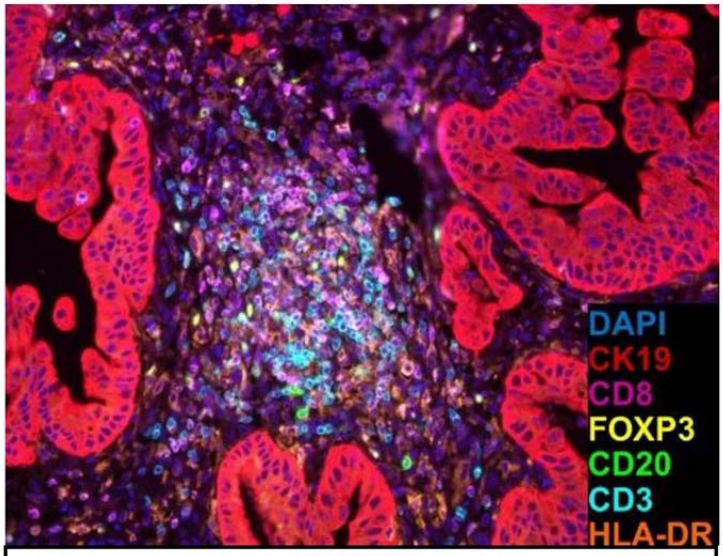


Fig 5. Immune tumor microenvironment from historical human pancreas tumor using multiplex immunofluorescence (qmIF) using antibodies targeting specific antigens which are indicated in legend.

. 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).

Sample Processing for $CD8^+$ T Cell Quantification

We believe that the combinations being tested, including atezolizumab combined with PEGPH20, compared to atezolizumab alone, will increase $CD8^+$ T cell infiltration within the tumor microenvironment.

A detailed protocol of tissue processing is provided in the laboratory manual. Tissue samples are to be sent to the address 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 allow for shipment delays which would 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: 212-851-4507
Alternate: 518-488-4704

7.1.2 Laser Capture Microdissection (LCM) and PDA

We hypothesize that PEGPH20 will change the regulatory context of PDA 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.

PDA tumors are characterized by two main components: the epithelium, formed from aggregates of tumor cells, and the surrounding stroma. Moffitt et al. 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, which they 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 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 and 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 **Error! Reference source not found.**, patients with the classical epithelial phenotype have significantly better prognoses as compared to basal-like phenotype [Kenneth Olive, submitted].

We hypothesize that the addition of PEGPH20 to atezolizumab, including other agents to be tested, compared to atezolizumab alone will result in gene regulation to enrich for 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 will be compared from distinct treatment groups to determine if certain treatments are able to alter the PDA epithelial gene expression from a basal/ECM-like to a classical/immune subtype which may confer a prognostic advantage. If a treatment(s) leads to enrichment for 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.

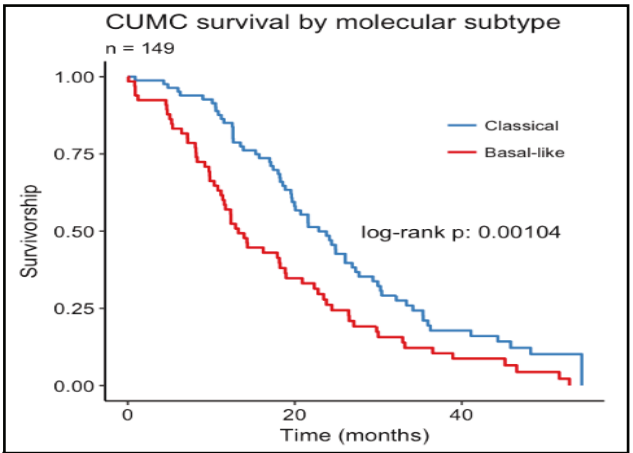


Figure 6. Kaplan-Meier survival by molecular subtype. VECTRA imaging of human PDA. Analysis of RNA-seq data from patients with resected PDA using epithelial classifiers shows differential prognosis among the

7.2 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 and will be sent to the Dr. Manji s laboratory for further processing 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 allow for shipment delays which would ensure timely delivery of bio-specimens.

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: 212-851-4507
Alternate: 518-488-4704

8. REGISTRATION PROCEDURES

8.1 CUMC RESEARCH PARTICIPANT REGISTRATION

Confirm eligibility as defined in the section Patient Selection and Withdrawal (Section 6).

Obtain informed consent, by following procedures along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent patients 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 patient enrolled on the study, in addition to providing the relevant source documentation to confirm patient eligibility.

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 patient 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.

Clinical Protocol & Data Management Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent Health Insurance Portability and Accountability Act (HIPAA) form, and demographics forms must be submitted to the Clinical Protocol & Data Management (CPDM) Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.304.6330, with the subject line **AAAS1908** Pending Patient Registration Request (PHI) . Upon receipt, applicable patient information and a pending eligibility status will be entered into Herbert Irving Comprehensive Cancer Center s (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 (ICF), including additional study ICFs for tissue.
- 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:

- The completed/signed study specific Eligibility Checklist (signed by a 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., complete blood count, complete metabolic panel, cholesterol and triglycerides pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
  - Copy of pathology and surgical reports
  - List of all prior malignancy-directed treatments
  - 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.).
  - Protocol deviation/waiver approvals (if applicable)

Please note: subject line of email or fax should include the following: AAAS1908 Complete Patient Registration Request (PHI) .

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed 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 Clinical Trial Management System (CTMS) database by the Central Registration Registrar. Upon completion, an official patient registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as patient ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible patients, as well as patient s who withdraw consent prior to enrollment 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.

9. TREATMENT PLAN

9.1 INVESTIGATIONAL AGENT ADMINISTRATION

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for treatment are described in Section 11. Appropriate dose modifications are described in Section 10 and Appendix 2 and Appendix 3. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be requested to maintain a medication diary if their treatment regimen contains an oral medication. The medication diary will be returned to clinic staff at the end of each treatment cycle.

9.1.1 Atezolizumab Administration

Atezolizumab will be administered at a fixed dose of 840 mg IV every 2 weeks (Q2W) (i.e. on Days 4 and 18 prior to surgery and on Days 1 and 15 of each 28 day cycle after surgery). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details) (Deng et al. 2016).

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, drug preparation, storage, and administration see the pharmacy manual and the Atezolizumab Investigator's Brochure. Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 2.

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. Standard anaphylaxis precautions should be taken when administering atezolizumab. Treatment for anaphylaxis will be administered per the instructions outlined below

Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided below and within Appendix 2.

Atezolizumab Treatment Interruption for Toxicities

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. Appropriate steroids supplementation should be provided if required prior to surgery in consultation with an endocrinologist and a pulmonologist in cases of pneumonitis. If atezolizumab is withheld for >12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the PI agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity with PI approval.

9.1.2 PEGPH20 Administration

PEGPH20 drug product supplied at a concentration of 0.30 mg/mL and will be supplied in a single-use vial that contains 1.0 mL. liquid formulation and should be stored at 2 C to 8 C before use. Stability testing of this PEGPH20 drug product was initiated and following general International Conference on Harmonisation (ICH) guidelines at 5 C – 3 C, and concurrent stability evaluation is ongoing. For additional details regarding formulation and handling of PEGPH20, please refer to pharmacy manual and PEGPH20 Investigator s Brochure.

PEGPH20 will be administered by IV infusion at a dose of 3μg/kg on Days 1 and 4 every week for 3 weeks prior to surgery and on Days 1, 8, and 15 every 28 days for 2 cycles after surgery. PEGPH20 will be administered 2-3 hours before the atezolizumab infusion.

PEGPH20 should be infused over 10−12 minutes, equivalent to approximately 1 mL/minute.

Piroxicam (20mg) will be administered 1-2 hours prior to PEGPH20 administration to minimize severe musculoskeletal events (MSE).

Prophylactic use of a proton-pump inhibitor (e.g., 20 mg omeprazole daily or over-the counter equivalent) is mandated for all patients while receiving PEGPH20.

Enoxaparin will be administered daily to all patients to minimize the risk of thromboembolic events (TE), a known complication of patients with pancreas adenocarcinoma and a known adverse event in PDA patients who receive PEGPH20. Enoxaparin will be administered by subcutaneous injection at a dose of 1 mg/kg/day rounding of dose may be done per institution policy and when using prefilled syringes. The dosage of enoxaparin will be based on the subject s screening weight and should be modified if the subject s weight changes by 10%. On days of dosing of PEGPH20, enoxaparin will be administered prior to infusion of PEGPH20. All efforts should be made to administer the calculated 1 mg/kg dose (– 10%). If prefilled syringes are used, the treating physician may use medical judgment regarding the appropriate prefilled syringe. However, if the rounded dose varies from the expected weight-based dose by 20% or more, the PI should be consulted. Refer to Table 3 for examples of rounding based on the expected enoxaparin dose. Enoxaparin should be held if the platelet count is <50,000 per mm^3 and should be resumed once the platelet count is greater than 50,000 per mm^3. The enoxaparin dose should be reduced to 0.5mg/kg for Grade 2 thrombocytopenia (platelet count 50,000 75,000 platelet per mm^3) until an increase in platelets > 75,000 platelet per mm^3, at which time the dose should be increased to

1mg/kg. Should a subject experience a TE event while on study, the dose of enoxaparin will be increased to a therapeutic dose based on standard clinical practice.

In situations when enoxaparin is held, administration of PEGPG20 should also be held during that period. Subjects who permanently discontinue enoxaparin therapy for any reason will also permanently discontinue PEGPH20. Likewise, enoxaparin treatment should be discontinued unless clinically indicated when the subject discontinues PEGPH20.

Table 3 Rounding Enoxaparin Doses

Expected Dose (mg)	Rounded Dose (mg)	Syringes Dispensed
35 – 49	40	40mg X1
50 – 69	60	60mg X1
70 – 89	80	80mg X1
90 – 109	100	100mg X1
110 – 134	120	120mg X1
135 – 164	150	150mg X1

PEGPH20 treatment interruption for Toxicities

PEGPH20 treatment may be interrupted for reasons other than toxicity with PI approval. The acceptable length of treatment interruption will be determined by the PI.

9.1.3 Atezolizumab in Combination with PEGPH20 Administration

Patients in the atezolizumab + PEGPH20 arm will receive treatment as outlined in Table 4 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). Treatment must be initiated no later than **5 days** after randomization.

Table 4 Treatment Cycle and Dosages

Cycle Length	Dose, Route, and Regimen (in order of administration)
28 days	**Pre-surgery** PEGPH20 3 μg/kg IV on Days 1, 4 [1] every week for 3 weeks Atezolizumab 840 mg IV on days 4 [1] and 18 **Post-surgery** PEGPH20 3 μg/kg IV on Days 1 [1], 8, and 15 every 28 days Atezolizumab 840 mg IV on days 1 [1] and 15

[1] On days where atezolizumab and PEGPH20 are administered, atezolizumab will be administered 2-3 hours after completion of the PEGPH20 infusion.

Atezolizumab in Combination with PEGPH20 Treatment Interruption for Toxicities

If atezolizumab is discontinued, PEGPH20 should also be discontinued. If PEGPH20 is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator in consultation with the PI. Refer to Appendix 3 for guidance.

The dose of PEGPH20 can be reduced to 1.6 μg/kg for management of drug-related toxicities. If further dose reduction is indicated, the patient must discontinue PEGPH20 but may continue treatment with atezolizumab if approved by the PI. After dose reduction, the dose of PEGPH20 may not be escalated.

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 > 12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the if the PI agrees that the patient is likely to derive clinical benefit. PEGPH20 treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If PEGPH20 is withheld for >21 days, the patient will be discontinued from PEGPH20. If the investigator believes the patient is likely to derive clinical benefit and the PI is in agreement, PEGPH20 treatment can be resumed after being withheld for > 21 days. If atezolizumab is discontinued, PEGPH20 should also be discontinued. If

PEGPH20 is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the PI.

Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezolizumab + PEGPH20 Arm

There will be no dose modifications for atezolizumab for the study. Guidelines for management of patients who experience specific adverse events are provided in Appendix 3.

ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZOLIZUMAB+PEGPH20 ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported to the PI immediately (i.e. no more than 24 hours after learning of the event).

Adverse events of special interest for the atezolizumab + PEGPH20 arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice. The finding of an elevated ALT or AST (> 3 baseline value) in combination with either an elevated total bilirubin (> 2 ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:
  - Treatment-emergent ALT or AST > 3 baseline value in combination with total bilirubin > 2 ULN (of which ≥35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 baseline value in combination with clinical jaundice. The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (AESI)
- Suspected transmission of an infectious agent by the study treatment, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis

- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barr syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation.
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- 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)
- Thromboembolic events
- Grade ≥3 musculoskeletal events persisting for >14 days

9.1.4 Adjuvant Chemotherapy

Surgical resection of the pancreas adenocarcinoma with negative margins represents the primary modality through which cure is achieved in patients with pancreatic cancer. As surgical techniques and expertise have evolved, increased long-term survival rates have been reported, however, it was not until 2007, when the results of the phase 3 CONKO-001 trial were published, that the role of adjuvant chemotherapy became firmly established (Oettle et al. 2007). In this randomized controlled phase 3 trial, patients were stratified 1:1 to chemotherapy, in which patients were to receive 6 cycles of gemcitabine given on Days 1, 8, and 15 every 4 weeks (n = 179), or observation (n = 175) following surgery. The trial demonstrated a median disease-free survival of 13.4 months in those receiving gemcitabine compared with 6.9 months in those who received no adjuvant therapy (95% confidence interval [CI], 6.1-7.8; P<0.001, log-rank). Long term follow-up of patients in this study demonstrated over a 10% difference in overall survival at 5 years (20.7% with gemcitabine versus 10.4% with observation) (Oettle et al. 2013). In 2010, gemcitabine was compared head-to-head with fluorouracil plus folinic acid in the randomized

controlled phase 3 European Study Group for Pancreatic Cancer (ESPAC)-3 trial (Neoptolemos et al. 2010). Patients with resectable pancreatic cancer were treated with either gemcitabine (n = 537) or fluorouracil plus folinic acid (n = 551) after surgery. The median overall survival was 23.6 months in those treated with gemcitabine and 23.0 months in those treated with fluorouracil plus folinic acid, however these results did not meet statistical significance (P = .39; HR, 0.94 [95% CI, 0.81-1.08]). Toxicity profiles significantly favored the use of gemcitabine compared to fluorouracil plus folinic acid. Regardless of the regimen used, these trials show a clear benefit to receiving adjuvant chemotherapy, and this practice has since become standard of care.

This approach, surgery followed by adjuvant chemotherapy, is also supported by several large systematic reviews. In one large meta-analysis, 951 pancreatic cancer patients were pooled from multiple randomized control trials in which patients were either treated with adjuvant chemotherapy or observed, and the addition of adjuvant chemotherapy prolonged the median survival time by 3 months and increased 5-year survival rates by 3.1% (Boeck et al. 2007). Another large meta-analysis of 875 patients showed reduction in the risk of death with chemotherapy by approximately 25% versus surgery alone. This study also demonstrated a doubling of the 5-year survival rates with adjuvant chemotherapy compared to observation (Stocken et al. 2005).

The phase 3 ESPAC-4 trial compared gemcitabine and capecitabine in the adjuvant setting compared to gemcitabine alone. The investigators reported an additional 2.5 month survival benefit with the addition of capecitabine to gemcitabine (28.0 months with gemcitabine plus capecitabine vs 25.5 months with gemcitabine alone, HR, 0.82 [95% CI, 0.68 0.98], p=0.032) (Neoptolemos et al. 2017). This combination is now being adopted given the overall survival benefit. However, within the United States, the doses used within the study are intolerable and require frequent dose and/or schedule modifications. It is likely that the frequent dose adjustments impact the efficacy of the combination to a degree which is currently unknown.

PRODIGE 24, a large randomized phase 3 study compared mFOLFIRINOX to gemcitabine monotherapy in the adjuvant setting and demonstrated a median overall survival benefit of 54.4 months compared to 35.0 months, respectively. 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). The reported 18-month overall survival (OS) is 67% with adjuvant gemcitabine in combination with capecitabine which is similar to the 63% reported when gemcitabine and oxaliplatin were tested in the neoadjuvant setting (O'Reilly et al. 2016). Although mFOLFIRINOX yielded impressive results, patients enrolled onto the study had a better performance status to withstand mFOLFIRINOX. Although SWOG S1313 indicated a

detrimental effect of adding pegylated recombinant human hyalouronidase (PEGPH20) to FOLFIRINOX compared to FOLFIRINOX alone, the current study is testing activity of PEGPH20 in combination with atezolizumab concurrently with subsequent treatment with mFOLFIRINOX which is distinct from concurrent therapy with PEGPH20 and mFOLFIRINOX as tested in SWOG S1313. Hence, we do not anticipate added risk to subjects who will be randomized to the atezolizumab and PEGPH20 cohort.

Table 5 Randomized Controlled Studies of Adjuvant Chemotherapy in Pancreatic Cancer

Trial	Inclusion Criteria	Treatment arms	N	DFS (mo.)	mOS (mo.)	3/5-year OS
CONKO-001 (2013)	• R0/R1 • Karnofsky PS >50% • CA19-9 <2.5x ULN	Observation Gemcitabine	175 179	6.7 13.4	20.2 22.8	5-year 10.4% (5.9–15.0) 20.7% (14.7–26.6) *p = 0.01*
ESPAC-4 (2017)	• R0/R1 • ECOG 0-2	Gemcitabine Gemcitabine and Capecitabine	365 366	13.9 13.1	28.0 25.5	5-year 28.8% (22.9–35.2) 16.3% (10.2–23.7) *p = 0.032*
PRODIGE 24 (2018)	• R0/R1 • ECOG 0-1 • CA19-9 <180 w/in 21d of starting rx	Gemcitabine mFOLFIRINOX	247 246	21.6 12.8	54.4 35	3-year 63.4% 48.6%

N = number; DFS = disease-free survival; OS = overall survival.

FOLFIRINOX

FOLFIRINOX is an alternative regimen for healthy individuals in the first-line setting. In a phase 2-3 randomized trial in patients with ECOG 0 or 1, FOLFIRINOX (Fluorouracil 400 mg/m2 as a bolus followed by 2400 mg/m2 given as a 46-hour continuous infusion, irinotecan 180 mg/m2, and oxaliplatin as 85 mg/m2, every 2 weeks) resulted in an 11.1 month overall survival compared to 6.8 months with gemcitabine a 4.3 month survival benefit over gemcitabine alone (HR 0.57; 95% CI, 0.37 to 0.59; P<0.001) (Conroy T, et al. 2011). Median PFS and objective response rate (RR) both favored FOLFIRINOX compared to gemcitabine alone; 6.4 months and 31.6% compared to 3.3 months and 9.4% in the group, respectively (P<0.001). One-year overall survival was 48.4% in the FOLFIRINOX arm versus 20.6% in the gemcitabine arm (Conroy T, et al. 2011). Although FOLFIRINOX is clearly superior to gemcitabine monotherapy, treatment is reserved for patients with excellent performance status due to its adverse event profile, which includes fatigue, bone marrow suppression with 45.7% grade 3 or 4 neutropenia, 12.7% diarrhea, and 9.0% sensory neuropathy. A follow-up of the PRODIGE 4/ACCORD

11 study indicated that efficacy was only mildly impacted in the 81% of the 242 patients who required dose reduction (mOS 10.9m versus 11.1m) (Metges JP, et al. 2014).

Due to poor tolerability of FOLFIRINOX in a significant proportion of patients, regimens with reduced doses of irinotecan and bolus fluorouracil, or omission of bolus fluorouracil, and addition of pegfilgastrim on day 3 or 4, commonly referred to as mFOLFIRINOX are widely used. mFOLFIRINOX resulted in a response rate of 30%, mPFS of 8.5 months, and mOS of 9.0 months in the 36 patients tested in the metastatic setting (Mahaseth H, et al. 2013). A prospective single arm phase 2 study tested the regimen with 25% dose reduction of bolus fluorouracil and irinotecan and found the RR, mPFS, and mOS to be 35.1%, 6.1 months, and 10.2 months respectively, which was comparable to that reported in the original PRODIGE 4/ACCORD 11 trial (Stein SM, et al. 2016). With the caveat of comparing distinct trials and limited number of patients, mFOLFIRINOX although better tolerated, may not be equivalent to full dose FOLFIRINOX when compared for efficacy, and it appears that the dose reduced forms have a shorter mOS. For patients who do not have a robust performance status or are intolerant to gem/*nab*-p, there may not be a choice but to use the dose-reduced regimen. Prophylactic administration of pegylated filgastrim in the absence of severe leukocytosis and pretreatment with palonosetron, aprepitant and dexamethasone likely contribute to a decrease in adverse events (Stein SM, et al. 2016). Pretreatment with atropine also appears to help with the cholinergic symptoms associated with Irinotecan. Other FOLFIRINOX modifications are described elsewhere (Marsh R, et al. 2015).

How to Administer

All patients will receive modified FOLFIRINOX (mFOLFIRINOX) on a 14 day +/- 3day cycle for 12 cycles.

General Instructions –

A. Subjects who experienced a reaction to oxaliplatin need to be re-challenged via hospitalization using desensitization protocol per local institution.
B. Subjects should be prescribed anti-emetics and antidiarrheal (loperamide) at home to be used on an as needed basis.
C. Subjects should be supplemented with pancreas enzymes if exhibiting signs of pancreas insufficiency.

Pre-treatment Medication –

D. Ondansetron 16mg oral once 30 minutes prior the initiation of chemotherapy
E. Dexamethasone 12mg oral once 30 minutes prior the initiation of chemotherapy (may be decreased by 50% if uncontrolled blood sugars)
F. Fosaprepitant 150mg IV once 30 minutes prior the initiation of chemotherapy
G. Atropine 0.5mg IV once 30 minutes prior the initiation of irinotecan if no contraindication which include but are not limited to
    a. Uncontrolled tachycardia
    b. Closed-angle glaucoma
    c. Pyloric obstruction
    d. Severe urinary retention or untreated prostatic hypertrophy
    e. Viscid plugs in patients with chronic lung disease.

mFOLFIRINOX –

A. Oxaliplatin 85 mg per square meter on day 1, IV infusion over 2 hours, followed by
B. Irinotecan 150 mg per square meter on day 1, IV infusion over 90 minutes to begin 30 min after leucovorin infusion is started (using a Y-tube);
C. Leucovorin 400 mg per square meter IV infusion over 2 hours
D. Fluorouracil 2400 mg per square meter IV continuous infusion over 46 hours (1200 mg/m /day)
E. Pegfilgastrim injector kit (6mg subcutaneous) on day 3

The investigational products will be prepared according to the institutional safety standards.

Dose Modification

If treatment cannot be given on a planned visit date, it may be administered +/- 3 days from the scheduled date.

Day 1 Dose Missed

If a dose was meant to be given on Day 1 was held or missed, the next cycle will not be considered to start until the day of the first dose which is actually administered.

Table 6 Dose Modification Table for Neutropenia/Thrombocytopenia

CBC on Day 15	Cycle Delay	Dose Reduction		
		Oxaliplatin	**Irinotecan**	**Fluorouracil – Leucovorin (5FU-LV)**
ANC ≥ 1.5 × 10^9/L and Platelet ≥100 ×10^9/L	No cycle delay	No dose reduction		
ANC < 1.5 × 10^9/L	Treatment delay until ANC ≥ 1.5 × 10^9 /L In case no recovery on D29, consider discontinuation of therapy or maintain 5FU-LV	1st Episode – no dose reduction 2nd Episode – reduce dose to 60mg/m2 3rd Episode – Discuss treatment discontinuation or maintain 5FU-LV	1st Episode – reduce dose to 120mg/m2 2nd Episode – maintain dose at 120mg/m2 3rd Episode – Discuss treatment discontinuation or maintain 5FU-LV	No dose reduction
Platelet < 100 ×10^9/L	Delay treatment until recovery In case no recovery on D29, consider discontinuation of therapy*	1st Episode – reduce dose to 60mg/m2 2nd Episode – maintain dose at 60mg/m2 3rd Episode – Discuss discontinuation*	1st Episode – no dose reduction 2nd Episode – reduce dose to 120mg/m2 3rd Episode – Discuss discontinuation	1st Episode – no dose reduction 2nd Episode – reduce dose to 1800mg/m2 IV continuous infusion

* To be discussed case by case with subject and principal investigator.

Table 7 Dose Modification Table for Neutropenia and Thrombocytopenia During Nadir

Event	Dose Reduction		
	Oxaliplatin	**Irinotecan**	**Fluorouracil – Leucovorin (5FU-LV)**
• **Febrile Neutropenia, or** • **≥ Grade 3 neutropenia with infection, or** • **Grade 4 neutropenia lasting > 7 days despite growth factor support**	1st Episode – no dose reduction 2nd Episode – reduce dose to 60mg/m^2 3rd Episode – discuss discontinuation*	1st Episode – reduce dose to 120mg/m^2 2nd Episode – maintain dose at 120mg/m^2 3rd Episode – discuss discontinuation*	1st Episode – no dose reduction 2nd Episode – no dose reduction 3rd Episode – consider monotherapy*
• **Bleeding, or** • **≥ Grade 3 thrombocytopenia**	1st Episode – reduce dose to 60mg/m^2 2nd Episode – maintain dose to 60mg/m^2 3rd Episode – discuss discontinuation*	1st Episode – no dose reduction 2nd Episode – reduce dose to 120mg/m^2 3rd Episode – discuss discontinuation*	1st Episode – no dose reduction 2nd Episode – reduce dose to 1800mg/m^2 3rd Episode – consider monotherapy*

* To be discussed case by case with subject and principal investigator.

Table 8 Dose Modification Table for Diarrhea

Diarrhea	Dose Reduction		
	Oxaliplatin	**Irinotecan**	**Fluorouracil – Leucovorin (5FU-LV)**
• **≥ Grade 3 or** • **With fever and/or ≥ Grade 3 neutropenia**	1st Episode – no dose reduction 2nd Episode – reduce dose to 60mg/m2 3rd Episode – maintain dose at 60mg/m2	1st Episode – reduce dose to 120mg/m2 2nd Episode – maintain dose at 120mg/m2 3rd Episode – Discuss treatment	1st Episode – no dose reduction 2nd Episode – reduce dose to 1800mg/m2 IV continuous infusion 3rd Episode – maintain dose at 1800mg/m2 IV continuous infusion
• **Persistent diarrhea for greater than 48 hours despite maximal loperamide support**	Recovery – no dose reduction	Recovery – no dose reduction	Recovery – no dose reduction

Table 9 Diarrhea Management Guidance

Diarrhea	Dose Reduction
	Oxaliplatin
• **One soft or liquid stool**	Instruct subject to take 2 capsules of loperamide immediately, and thereafter 1 capsule after each unformed stool for a maximum of 16mg per day.
• **Persistent diarrhea for greater than 48 hours despite maximal loperamide support**	Subject should be evaluated to rule out *clostridium difficile* and then initiated on adjunctive therapies with broad spectrum antibiotics or replaced by another antidiarrheal at the clinical investigator's choice. Consider testing for UGT1A and dihydropyrimidine dehydrogenase (DPD) deficiency.
• **Persistent and/or severe diarrhea despite administration of two anti-diarrheal therapy**	Subject should be hospitalized for hydration and tested for UGT1A and DPD deficiency, particularly in setting of other toxicities. Rule out *clostridium difficile* and subsequently initiate diphenoxylate-atropine, octreotide, or tincture of opium. Consider evaluation by a gastroenterologist.

Table 10 Dose Modification Table for Peripheral Neuropathy

Event	Duration of Peripheral Neuropathy		
	≤7 days	**> 7 and < 14 days**	**Persistent**
Grade 1 – Mild paresthesias without any compromise in function	no dose reduction	no dose reduction	no dose reduction
Grade 2 – Mild to moderate objective sensory loss without affecting activities of daily living	no dose reduction	no dose reduction	reduce dose to 60mg/m2
Grade 3 – Parasthesia with pain and functional compromise impacting activities of daily living	reduce dose to 60mg/m2	reduce dose to 60mg/m2	permanently discontinue
Acute laryngopharyngeal dysesthesia	• Prolong infusion duration to 6 hours. • Add 1gram of calcium gluconate and 1 gram of magnesium sulfate over 15 minutes before and after oxaliplatin infusion.		

Mucositis and Hand-Foot Syndrome –

Reduce 5FU-LV dose by 25% for the remaining treatment duration.

Cardiotoxicity –

Permanently discontinue 5FU-LV treatment for the remaining treatment duration.

Hyperbilirubinemia –

Rule out tumor recurrence if total bilirubin is > 1.5 of upper limit of normal. Hold irinotecan and consider investigational studies to rule out biliary obstruction. Hold irinotecan if total bilirubin persistently elevated > 1.5 of upper limit of normal.

9.1.5 Cautionary Therapy

Systemic corticosteroids and tumor necrosis factor α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, patient will not meet eligibility criteria.

9 . 2 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Permitted Therapy for Atezolizumab and PEGPH20

- Oral contraceptives
- Hormone-replacement therapy
- 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
- Hormonal therapy with gonadotropin−releasing hormone agonists or antagonists for prostate cancer

- Ketorolac for severe pain Ketorolac may be given for severe pain as recommended in the prescribing information. Ketorolac should not be administered on the same day as piroxicam or other nonsteroidal anti-inflammatory drugs (NSAIDs) because of the cumulative risk of inducing serious NSAID-related side effects.
- Prescription medications such as narcotics, muscle relaxants, NSAIDs and other analgesics (with the exception of corticosteroids), over-the-counter drugs, and physical therapy for treatment of MSEs, at the investigator's discretion NSAIDs should not be administered on the same day as piroxicam.
- Intravenous heparin for acute treatment of TE events. Only PEGPH20 must be withheld while the patient is receiving intravenous heparin.
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and PEGPH20 may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anti-convulsant therapy, if required, is administered at a stable dose.

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 doses of adjuvant chemotherapy. However, at the discretion of the investigator, hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of study treatment.

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 β_2- adrenergic agonists; see Appendix 2).

Prohibited Therapy for Atezolizumab+PEGPH20 Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority−approved or experimental, is prohibited, and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- 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 4 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.
- Chronic use of intravenous heparin is prohibited during treatment with PEGPH20. However, intravenous heparin may be given for acute treatment of TE events.
- Megestrol acetate is prohibited within 10 days prior to initiation of PEGPH20 and during treatment with PEGPH20.

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 PI if questions arise regarding medications not listed above.

Risks Associated with PEGPH20

Please refer to the must updated PEGPH20 IB. Identified risks for PEGPH20 include MSEs such as myalgia and arthralgia, infusion-related reactions, and TE events see below). Refer to the PEGPH20 Investigator's Brochure for a detailed description of all anticipated risks for PEGPH20.

Musculoskeletal Events (MSEs)

The majority of treatment-related adverse events have been MSEs. The severity of the MSEs appeared to be influenced by the dose and dosing frequency of PEGPH20. In general, symptoms tended to be more severe with higher doses of PEGPH20 and a more frequent dosing schedule. At the highest doses tested in humans (50 g/kg), Grade 3 or 4 MSEs occurred approximately 4−10 hours after the first dose. Reported MSEs include, but are not limited to, muscle spasms, arthralgia, myalgia, muscular weakness, pain in extremity, back pain, bone pain, musculoskeletal pain, joint swelling, joint stiffness, limb discomfort, musculoskeletal stiffness, myositis, and neck pain. Treatment with dexamethasone has been used to attenuate the severity of MSEs, improving the tolerability of higher PEGPH20 dose and dosing frequency combinations. However, given that corticosteroid treatment (i.e., dexamethasone) may potentially interfere with the efficacy of atezolizumab, treatment with NSAIDs is being used instead of corticosteroids in this study. Piroxicam and ketorolac have been investigated in an animal model of MSEs and may be helpful in decreasing the severity of MSEs in patients (Halozyme internal unpublished report). In this study, piroxicam will therefore be administered as premedication to decrease the severity of MSEs. Ketorolac may be given for severe pain per the prescribing information. Ketorolac and other NSAIDs should not be administered on the same day as piroxicam.

Thromboembolic Events (TE)

TE events and, more frequently, venous TE events, are reported to occur with higher frequency in patients with pancreatic cancer. The PEGPH20 Investigator's Brochure indicates that patients with a history of cerebrovascular accident, deep vein thrombosis, or pulmonary embolism, or a history or evidence of carotid artery disease are not eligible to participate in PEGPH20 clinical studies. Patients will be treated prophylactically with subcutaneous enoxaparin to reduce the risk of TE events. It is well documented that the use of megestrol acetate causes thrombosis; therefore, concomitant use of megestrol acetate is prohibited during treatment with PEGPH20.

NOTE: Thromboembolic events are considered AEs of special interest. All TE events, regardless of type of event, severity, or seriousness must be reported to Halozyme within 5 calendar days of receipt by the sponsor-investigator.

Risks Associated with Combination Use of Atezolizumab and PEGPH20

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and PEGPH20:

- **Infusion-related Reactions**
- **Musculoskeletal Events**

9.3 DURATION OF THERAPY

Patients will receive two doses of atezolizumab prior to surgery (3 weeks and 1 week prior to surgery) and four doses post- surgery every 2 weeks after recovery from surgery (starting between 4 and 6 weeks post-surgery). Patients randomized to the atezolizumab + PEGPH20 arm will receive PEGPH20 for 3 weeks prior to surgery and for two cycles after recovery from surgery.

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

- Disease recurrence
- Therapy may be permitted beyond recurrence if patient is deriving clinical benefit after initial tumor growth or ambiguity regarding the existence of disease recurrence in consultation with the Principle Investigator (PI) and Sponsor. If subsequent imaging confirms tumor growth, recurrence will be back dated to the prior scan. If patient agrees to treatment beyond recurrence, the patient will be required to sign a Treatment Beyond Recurrence informed consent form. Biopsy of the lesion demonstrating recurrence will be required to determine histologic disease recurrence, unless it is unsafe to do so. In case where a biopsy is not possible, data from rise in tumor markers and/or enlarging size of lesion on repeat imaging in 6 weeks (+/- 2 weeks) will be used to adjudicate recurrence by the treating physician in consultation with the PI.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

- Major protocol violation

9.4 TUMOR SAMPLE ANALYSIS

Tumor specimens will be collected, processed and analyzed as described previously (Section 7).

9.4.1 Biopsy Samples

Biopsy samples will be collected by EUS by a highly experienced interventional gastroenterologist using standardized technique. EUS can visualize the primary pancreas mass, the surrounding pancreas anatomy, and subsequently localization of the interposing vessels by applying Doppler signal. The EUS will guide the angle of puncture without causing vascular injury in hopes to obtain core tissue. Multiple core tissue samples (at least four if clinically safe) will be obtained and processed in the following order of importance for analysis which will be dependent by the amount of evaluable cores

a) 1 core - Formalin fixed paraffin embedded tissue

b) 2 cores -Fresh frozen × 2

c) 1 core - FLOW cytometry

Please refer to corresponding laboratory manual for instructions to process the specimens.

9.4.2 Resected Tumor Sample

At the time of surgery, four random core biopsies from the tumor will be obtained by the surgeon performing the PDA resection by direct visualization and cores processed as in Section 9.4.1 above. These samples will be analyzed for multiplex immunofluorescence and laser capture microdissection as described in Section 7.1. Standard of care microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) will be performed by the treating institution.

9.4.3 Blood Samples

Patients will undergo serial blood collection within 6 hours of initiation of investigative therapy, within 6 hours prior to surgical resection, time of beginning of each cycle of investigative adjuvant therapy (within 6 hours prior to start of therapy), beginning of adjuvant chemotherapy (within 6 hours prior to start of therapy), and at the start of Cycle 4 of adjuvant chemotherapy (within 6 hours prior to start of therapy, see Table).

All samples will be sent to Dr. Manji s laboratory

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: 212-851-4507
Alternate: 518-488-4704

Duration of Follow Up

Patients will be followed after study completion or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Thereafter, patients will be contacted by phone/in person every 3-4 months during the first 3 years and every 6 months thereafter to obtain information about subsequent treatment(s) and survival status.

9.5 CRITERIA FOR REMOVAL FROM STUDY

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse event, clinically significant disease recurrence, patient request, investigator decision, deemed surgically inoperable for any reason, major protocol violation such that patient is deemed not suitable to continue therapy, patient noncompliance, and study termination by the Sponsor or IRB/ IEC. When a patient discontinues or is withdrawn, the investigator will notify the Sponsor and should perform the procedures indicated in the End of Study column in the Schedule of Events within 28 days after discontinuation of study drug and before initiation of any new anti-cancer therapy. Follow-up information will be obtained for patients who discontinue their participation in or are withdrawn from the study.

Patients withdrawn from the study for reasons other than toxicity or clinically significant disease recurrence (e.g., protocol violation or noncompliance) may be replaced at the discretion of the PI and the investigator. Study drug administration may be discontinued for an adverse event or at the discretion of the investigator.

The consequence of withdrawal of all consent by a patient will be that no new information will be collected from that patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety.

10. DOSE ADMINISTRATION AND MODIFICATIONS

Guidelines for dose administration for the following cohorts are provided in Table 11 and Table 12.

Table 11 Dose Administration (Atezolizumab alone)

Cycle Length	Dose, Route, and Regimen (in order of administration)
28 days	**Pre-surgery –** Atezolizumab 840 mg IV on days 4 and 18 **Post-surgery –** Atezolizumab 840 mg IV on days 1 and 15 for 2 cycles

Dose Modifications for Management of Atezolizumab-Specific Adverse Events

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 $\geq$1 month to $\leq$ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for $>$ 12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$ 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$ 12 weeks if the PI 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 PI. Please refer to Appendix 2 for management of atezolizumab-related adverse events.

Table 12 Dose Administration (Atezolizumab + PEGPH20)

Cycle Length	Dose, Route, and Regimen (in order of administration)
28 days	**Pre-surgery –** Atezolizumab 840 mg IV on days 4 [1] and 18 PEGPH20 3 μg/kg IV on Days 1, 4 [1] every week for 3 weeks **Post-surgery –** Atezolizumab 840 mg IV on days 1 [1] and 15 for 2 cycles PEGPH20 3 μg/kg IV on Days 1 [1], 8, and 15 every 28 days

[1] On days where atezolizumab and PEGPH20 are administered, atezolizumab will be administered 2-3 hours after completion of the PEGPH20 infusion.

Dose Modifications and Management of PEGPH20 and Atezolizumab-Specific Adverse Events

Please refer to Appendix 3 for management of adverse events for the PEGPH20 + atezolizumab arm.

11. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

11.1 SAFETY OF ATEZOLIZUMAB IN HUMANS

As of 17 May 2018, > 16,000 patients with solid tumors or hematologic malignancies have received atezolizumab as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy through participation in a clinical trial. Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events (AEs) have been determined. Among 3075 patients treated with single-agent atezolizumab for whom pooled safety data are available, the most commonly reported AEs (≥ 10%) include fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea, pyrexia, vomiting, arthralgia, back pain, asthenia, anemia, pruritus, rash, headache, and peripheral edema.

The AEs observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of the individual study treatment. Systemic immune activation, characterized by an excessive immune response, is a potential risk associated with atezolizumab when used in combination with another immunomodulating compound. Atezolizumab-related AEs were comparable between patients who received atezolizumab monotherapy and those who were treated with atezolizumab in combination with targeted therapy and/or chemotherapy. There are no atezolizumab-related AEs that are exacerbated when used in combination with other agents.

Immune-related AEs are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related AEs are closely monitored during the atezolizumab clinical program. Immune-related AEs associated with atezolizumab include pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barr syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis and nephritis.

Study GP28363 is evaluating combination cobimetinib and atezolizumab in patients with locally advanced or metastatic solid tumors. As of 4 September 2017, there were 150 safety-evaluable patients with tumor types including colorectal cancer, metastatic melanoma, and NSCLC who were on different treatment regimens of atezolizumab + cobimetinib.

Of the 150 safety-evaluable patients, 148 (98.7%) experienced an adverse event. The most frequently observed AEs (≥ 30%) were diarrhea (70.7%), fatigue (56.7%), rash (48%), vomiting (43.3%), nausea (36.7%), constipation (30%) and abdominal pain (22.7%). Adverse events assessed as related to atezolizumab were reported in 117patients (78.0%). The most common such AEs (≥ 10%) were fatigue (31.3%), diarrhea (28.0%), pruritus (14.0%), rash (13.3%), and nausea (12.7%), vomiting (10.0%), pyrexia (10.0%)

These findings are consistent with the known adverse event profiles for atezolizumab and cobimetinib and did not represent additive toxicity.

Grade 3–4 AEs were observed in 99 (66.0%) of the patients, and the most common (≥ 2.7% or ≥ 4 patients) included fatigue (10.7%), anemia (10.0%), diarrhea (8.7%%), abdominal pain and blood creatinine phosphokinase increased (5.3% each), rash (4.7%), dyspnea, aspartate aminotransferase increased amylase increased and hypertension (4% each), and ascites, vomiting, peripheral edema, pleural effusion,

pulmonary embolism, blood bilirubin increased, lipase increased, neutrophil count decreased, hyponatraemia, and hypophosphatemia (2.7% each Most of the Grade 3–4 AEs considered related to atezolizumab were single reports except for fatigue (3.3%), rash (2.7%), diarrhea (2%), amylase increase (2.7%), lipase increased and anaemia (2%), dermatitis acneiform, nausea, vomiting, dyspnea, aspartate aminotransferase increase and neutrophil count decrease (1.3% each).

Six patients (4%) were reported to have had Grade 5 AEs. The following events led to death in 6 patients (4.0%): pneumonia, large intestine perforation, small intestinal obstruction, sepsis, road traffic accident, and respiratory failure. The event of sepsis was the only Grade 5 event considered related to atezolizumab. In this case, the patient had a medical history of infectious disease (right temporal lobe abscess).

Sixty-nine safety-evaluable patients (46%) had a serious adverse event, most of which were single reports. The exceptions were pneumonia (6%), pyrexia and dyspnea (4% each), abdominal pain (3.3%), vomiting and sepsis (2.7%), fatigue, pulmonary embolism (2% each), and bacteremia, cellulitis, lung infection, ascites, intestinal obstruction, nausea, peripheral edema, pain, pleural effusion, pneumonitis, dehydration, and fall (1.3% each).

Twenty-three safety-evaluable patients (15.3%) experienced an adverse event leading to discontinuation from atezolizumab.

Reproductive and developmental toxicity studies with atezolizumab have not been conducted. The PD-L1/PD-1 signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation (Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011). Administration of atezolizumab is expected to have an adverse effect on pregnancy via modulation of maternal/fetal tolerance, and poses a risk to the human fetus, including embryo-lethality via an increased risk of immune-mediated rejection.

Other possible consequences of inhibiting the PD1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in dysregulated immune defenses and is currently a theoretical risk.

Table 13 Serious Adverse Drug Reactions for Atezolizumab in All Indications Considered Expected for Safety Reporting Purposes

Please refer to the current IB Version for a complete list for safety of atezolizumab.

SOC	SADRs (MedDRA Preferred Terms)	Total number of patients = 3075		
		Patient No. (%)	No. of life-threatening events*	No. of fatal events
General disorders and administration site conditions	Asthenia	454 (14.8%)	N/A	N/A
	Malaise	76 (2.5%)	N/A	N/A
	Fatigue	1093 (35.5%)	N/A	N/A
	Influenza-like illness	180 (5.9%)	N/A	N/A
	Pyrexia	613 (19.9%)	N/A	N/A
Respiratory, thoracic and mediastinal disorders	Dyspnoea	635 (20.7%)	N/A	N/A
	Hypoxia	72 (2.3%)	N/A	N/A
	Interstitial lung disease	4 (0.1%)	N/A	N/A
	Pneumonitis	69 (2.2%)	N/A	N/A
Gastrointestinal disorder	Colitis	34 (1.1%)	N/A	N/A
	Diarrhoea	607 (19.7%)	N/A	N/A
	Dysgeusia	82 (2.7%)	N/A	N/A
	Nausea	728 (23.7%)	N/A	N/A
	Vomiting	471 (15.3%)	N/A	N/A
Investigation	Alanine aminotransferase increased	160 (5.2%)	N/A	N/A
	Aspartate aminotransferase increased	173 (5.6%)	N/A	N/A
	Blood bilirubin increased	51 (1.7%)	N/A	N/A
Metabolism and nutrition disorders	Diabetes mellitus	7 (0.2%)	N/A	N/A
	Hyperglycaemia	90 (2.9%)	N/A	N/A
	Hyponatraemia	163 (5.3%)	N/A	N/A
Musculoskeletal and connective tissue disorders	Muscular weakness	103 (3.3%)	N/A	N/A
	Back pain	471 (15.3%)	N/A	N/A
	Bone pain	89 (2.9%)	N/A	N/A

SOC	SADRs (MedDRA Preferred Terms)	Total number of patients = 3075		
		Patient No. (%)	No. of life-threatening events*	No. of fatal events
Skin and subcutaneous tissue disorders	Rash	337 (11.0%)	N/A	N/A
	Rash maculo-papular	77 (2.5%)	N/A	N/A
Infections and infestations	Encephalopathy	6 (0.2%)	N/A	N/A
	Meningitis	5 (0.2%)	N/A	N/A
	Urinary tract infections	311 (10.8%)	N/A	N/A
Endocrine disorders	Hypothyroidism	126 (4.1%)	N/A	N/A
Immune system disorders	Hypersensitivity	35 (1.1%)	N/A	N/A
Hepatobiliary disorders	Hepatitis	306 (10.0%)	N/A	N/A
Injury, poisoning and procedural complications	Infusion related reaction	4 (0.1%)	N/A	N/A

N* = number of patients who experienced the SADR

N/A: fatal or life-threatening SADR are not considered expected.

All fatal or life-threatening SADRs are considered unexpected for regulatory reporting purposes.

AE = adverse event;SAE = serious adverse event; SOC = System Organ Class.

Grade 5 AEs due to PD are excluded for studies GO27831 and GO28625. Investigator text for AEs encoded using MedDRA v20.1. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Percentages are based on number in the column headings. AEs collected after first treatment dose are included. Adverse events with missing grade are not included.

Clinical cutoff dates: GO27831 (31 March 2016), GO28625 (7 January 2015), GO28753 (1 December 2015), GO28754 (1 December 2015), GO29293 (4 July 2016), GO28915 (7 July 2016), and GO29294 (13 March 2017). December 2015), GO28754 (1 December 2015), GO29293 (4 July 2016), GO28915 (7 July 2016), and GO29294 (13 March 2017).

Immune-related myositis, nephritis, uveitis, myopathies, and cardiac toxicities, which can be serious, have also been reported.

CONTRAINDICATIONS

Atezolizumab is contraindicated for patients with the following:

a) History of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins.

b) Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.

WARNINGS AND PRECAUTIONS

The warnings and precautions for atezolizumab are listed below. Management guidelines are listed in Appendix 2 which include specific guidelines for

a) Immune-related hepatitis

b) Immune-related colitis

c) Immune-related pneumonitis

d) Immune-related pancreatitis

e) Immune-related endocrinopathies (i.e., diabetes mellitus, hypothyroidism. hyperthyroidism, adrenal insufficiency, hypophysitis)

f) Immune-related meningoencephalitis

g) Immune-related neuropathies (i.e., myasthenic syndrome/myasthenia gravis, Guillain-Barr syndrome)

h) Immune-mediated nephritis

i) Immune-related myocarditis

j) Myositis

k) Infusion-related reactions

Immune-related adverse events remain the major safety concern for atezolizumab, as is the case with other agents in this class.

11.2 SAFETY OF PEGPH20

The following adverse events are classified as identified risks associated with PEGPH20: Neutropenia, thrombocytopenia, peripheral edema, infusion-related reaction, pulmonary embolism, deep vein thrombosis, cerebrovascular accident, mesenteric vein thrombosis, myocardial infarction, vena cava thrombosis, venous thrombosis, muscle spasms, arthralgia, myalgia, muscular weakness, back pain, musculoskeletal pain, and pneumonia. Please refer to the current IB for the most updated adverse events for PEGPH20.

Please refer to the current IB Version for a complete list for safety of PEGPH20.

The overall safety analysis from HALO-109-202 study in patients with stage IV PDA who were treated with gemcitabine, nab-paclitaxel, and PEGPH20 in a phase 2 study confirmed musckulosekeletal events (MSEs; primarily grade 1 or 2 severity), thromboembolic events, and infusion-related reactions. Additionally, adverse. Trials combining immune check point blockade and PEGPH20 are ongoing with limited data available.

Musculoskeletal events are an important identified risk due to their high frequency and the need to premedicate (with dexamethasone or NSAIDs as specified in the study protocols) to ameliorate their intensity. These events include but are not limited to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) such as muscle spasms, arthralgia, myalgia, muscular weakness, pain in extremity, back pain, bone pain, musculoskeletal pain, joint swelling, joint stiffness, limb discomfort, musculoskeletal stiffness, myositis, and neck pain. While the incidence across the clinical studies has been ≥75%, the events were mostly Grade 1/2 in severity, nonserious, and infrequently led to study treatment discontinuation. Musculoskeletal events continue to be observed very commonly in PEGPH20-treated patients. These events are managed by the administration of dexamethasone in ongoing studies, with the exception of the administration of piroxicam in studies with immunotherapies (as administered in HALO-107-101) due to the potential effect of steroids on efficacy. The dexamethasone and piroxicam prophylaxis appears to attenuate the severity of these events.

Thromboembolic events (TEs) and their sequelae have been observed in clinical studies evaluating PEGPH20 combination therapies in patients with pancreatic cancer, NSCLC, and gastric cancer. It is widely accepted that PDA and gastric cancer are tumor types with a high TE event background rate. The observed events were mainly of venous origin and included PTs such as pulmonary embolism, thrombosis, embolism, mesenteric vein thrombosis, DVT, jugular vein thrombosis, and venous thrombosis. Arterial events have also been observed but less frequently than venous events and include PTs such as cerebral ischemia, cerebrovascular accident, splenic infarction, basal ganglia infarction, and myocardial infarction. Due to the risks of increased TE, all patients treated with PEGPH20 will also receive anticoagulation.

Infusion-related reactions remain an identified risk of PEGPH20 although their overall incidence remains low (<5%). This risk was initially identified in Study HALO-109-201 when PEGPH20 was initially administered either by IV push or over 4-5 minutes. Current protocol instructions require that PEGPH20 be administered by a slow IV infusion over 10 minutes. This risk is being mitigated by administering PEGPH20 over 10 minutes as well as excluding patients with a known allergy to hyaluronidase.

11.3 SAFETY DEFINITONS

ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern

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 adverse events 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

Note: This includes the following:

- 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 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** for all adverse event reporting criteria.

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v. 5) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

Note: Based on the most recent version of NCI CTCAE 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

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.

Serious Adverse Event:

Adverse events 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 pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - 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

  Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the patient, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Adverse Events of Special Interest

Certain events are considered AEs of special interest. All events of special interest, regardless of type of event, severity, or seriousness must be reported within 5 calendar days of receipt by the sponsor-investigator. Please see section S11.5 for a complete list.

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 all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval 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.

11.4 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

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

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. 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.** After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

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

suspected relationship to atezolizumab and/or PEGPH20 (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 the atezolizumab and/or PEGPH20, and the AE cannot be readily explained by the patient s clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the atezolizumab and/or PEGPH20; and/or the AE abates or resolves upon discontinuation of the atezolizumab and/or PEGPH20 or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the atezolizumab and/or PEGPH20 (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab and/or PEGPH20 administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure (I.B).

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

11.5 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

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

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

Specific Instructions for Recording Adverse Events

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

a. 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.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 11.4), 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 .

c. 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).

d. Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

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

e. 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 atezolizumab and/or PEGPH20 should be reported as an SAE.

f. 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 atezolizumab and/or PEGPH20. 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 adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event 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.

g. 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, and 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 require active management, the suspected cause and course of management should also be documented.

i. Adverse Events of Special Interest to be Reported Immediately to the Sponsor/Collaborator: Genentech/Roche

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.

Adverse events listed below are required to be reported by the investigator to Genentech, Inc. immediately (< 48 hours, excluding holidays and weekends, after learning of the event). Affiliate sites should report directly to CUMC, who will report to Genentech on behalf of Affiliate sites.

Adverse events of special interest for the atezolizumab or atezolizumab + PEGPH20 arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, and based on the following observations:
  - Treatment-emergent ALT or AST > 3X baseline value in combination with total bilirubin > 2 X upper limit of normal (ULN), of which ≥ 35% is direct bilirubin
  - Treatment-emergent ALT or AST > 3 X baseline value in combination with clinical jaundice

The atezolizumab Events of Special Interest are:

The following AEs are considered of special interest and must be reported to the FCCC Investigator-Sponsored Research Unit (ISRU) (SAE.FCCC@fccc.edu) within 24 hours of the awareness date and must be reported to the Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barr syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis

- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade > 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

The PEGPH20 adverse events of special interest are as follows:

- Musculoskeletal events:
- Myalgia
- Muscle spasms
- Arthralgia
- Bone pain
- Musculoskeletal chest pain
- Joint stiffness
- Muscular weakness
- Musculoskeletal pain

j. 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 and pregnancy reports originating from the Study for atezolizumab and PEGPH20. Investigators must report all SAEs 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

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

And to **HALOZYME's** Drug Safety Department at: safety@halozyme.com

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 and to Halozyme. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below for both Genentech/Roche and Halozyme:

Reporting to Genentech/Roche:

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), 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 either electronically or by fax and within the timelines specified below:

- **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.

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

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

- **Other SAEs**

Serious AE reports that are unrelated to the Product shall be transmitted to Roche 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 Roche 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.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESI reporting to Roche**

AESIs requiring expedited reporting shall be forwarded to Roche within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.

- **Special situation reports**

In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Roche 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)
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected
- Lack of therapeutic efficacy
- Drug interaction
- Use of a Medicinal Product in a Pediatric and Elderly population (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.

Reporting to Halozyme:

All SAEs, initial and follow-up versions of the case, should be reported to Halozyme within 5 calendar days of receipt by the Investigator-Sponsor.

In addition, the Investigator-Sponsor must provide Halozyme Drug Safety with a copy of any FDA submissions of the following within 24 hours of submission:

- Expedited (7-day or 15-day) initial and follow-up safety reports
- IND annual reports/Development Safety Update Report (DSUR)

All SAE information exchanges between the Investigator-Sponsor to Halozyme Drug Safety will be completed within 30 calendar days after closure of the study database.

For any recurring, non-serious safety issues involving possible risk to subjects, notify Halozyme s Drug Safety Department within 5 calendar days of the Investigator-Sponsor s initial awareness.

Halozyme may request additional information or clarification of details for a particular event. The Investigator-Sponsor must respond to such a request within a reasonable amount of time, or more rapidly if the request is identified as urgent.

Sponsor-Investigator must provide a cumulative listing of AEs to the Halozyme Drug Safety Department on a monthly basis unless otherwise requested by Halozyme. This listing must include all AEs that have occurred from the start of the study by treatment arm. At a minimum, the listing should include the following data for each AE: verbatim term; start date; stop date; serious AE (SAE) criterion met, if applicable (i.e., death, life-threatening, hospitalization - admission or prolongation, persistent or significant disability or incapacity, congenital anomaly or birth defect, or other important medical event); severity (grade according to NCI CTCAE criteria); relationship to each study medication (causality assessment); actions taken as a result of the AE (e.g., none, concomitant medication, non-drug therapy, study drug discontinuation, study drug suspended and restarted, discontinuation from study due to AE, etc.); and outcome.

AESI reporting to Halozyme

Thromboembolic events are considered AEs of special interest. All TE events, regardless of type of event, severity, or seriousness must be reported to Halozyme within 5 calendar days of receipt by the sponsor-investigator.

k. Reporting to Regulatory Authorities, Ethics Committees and Investigators

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.

Genentech will be responsible for the expedited reporting of safety reports originating from the Study to the European Medicines Agency (EMA) through Eudravigilance Clinical Trial Module (EVCTM).

Sponsor will be responsible for the distribution of safety information to its own investigators, where relevant.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator s assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/downloads/AboutFDA/ReportsManualsFo rms/Forms/UCM048334.pdf

Additional Reporting Requirements for IND Holders (if applicable):

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR §600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The PI 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 atezolizumab and PEGPH20. An unexpected adverse event is one that is not already described in the Atezolizumab and PEGPH20 Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and collaborators Genentech/Roche and Halozyme within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The PI 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 atezolizumab and PEGPH20. An unexpected adverse event is one that is not already described in the PEGPH20 IB.

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/Roche and Halozyme, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech/Roche Drug Safety and emailed to Halozyme Drug Safety:

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

Halozyme – safety@halozyme.com

Investigator will be responsible for the distribution of safety information to Site IRB per local policies and procedures:

CUMC-Specific IRB SAE and Unanticipated Problem (UP) reporting requirements:

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at CUMC or affiliate sites. CUMC will report to the HICCC DSMC on behalf of affiliate sites. **For Affiliate Site reporting guidelines, please refer to Section 19.8. All SAEs from affiliate sites should be reported directly to CUMC.**

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to patients or others must be submitted to the IRB within 1 week (5 business days) following the occurrence of the unanticipated problem or the PI 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.

Affiliate Sites should direct safety reporting questions to the CUMC Sponsor-Investigator and Multicenter Core.

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

Tel: (888) 835-2555

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

And Halozyme Drug Safety:

safety@halozyme.com

AGGREGATE REPORTS

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to the collaborators, Genentech, and Halozyme.

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

Other Reports

Sponsor will forward a copy of the Publication to collaborators Genentech/Roche and Halozyme upon completion of the Study.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to collaborators Genentech and Halozyme. 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 and Halozyme. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Atezolizumab IIS Clinical Operations: anti-pdl-1-mpd3280a-gsur@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 CUMC. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. Any additional agreements between CUMC and study collaborators, Genentech/Roche, and Halozyme will be outlined in the Clinical Trials Agreement.

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.

Any additional agreements between CUMC and study collaborators, Genentech/Roche, and Halozyme will be outlined in the Clinical Trials Agreement.

12. PHARMACEUTICAL INFORMATION

12.1 TREATMENT REGIMEN

12.1.1 Atezolizumab

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in CHO cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to

Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets PD-L1 and inhibits its interaction with its receptor, PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells. It is administered as an IV formulation.

For further details, see the Atezolizumab Investigator s Brochure.

12.2 METHOD FOR ASSIGNING PATIENTS TO TREATMENT GROUPS

Randomization:

At randomization, patients will be assigned to one of the two cohorts in a 1:1 ratio: **Cohort 1)** Atezolizumab **or Cohort 2)** Atezolizumab + PEGPH20.

12.3 PREPARATION AND ADMINISTRATION OF STUDY DRUG

Atezolizumab and PEGPH20 are prepared according to the recommendations from the manufacturers label. Atezolizumab and PEGPH20are supplied by Roche/Genentech and Halozyme, respectively.

12.3.1 PEGPH20

Patients will receive PEGPH20 will be administered at 3μg/kg IV on Days 1 and 4 weekly for 3 weeks prior to surgery and on Days 1, 8, and 15 on a 28 cycle for 2 cycles after surgery. Missed doses will not be made up.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Appendix 3.

12.3.2 Atezolizumab

Atezolizumab will be administered on Days 4 and 18 prior to surgery and on Days 1 and 15 on a 28 day cycle for 2 cycles after surgery.

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 14). 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.

Table 14 Administration of First and Subsequent Atezolizumab Infusions.

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, 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 during the infusion at 15, 30, 45, and 60 minutes (+/- 5 minutes for all time points) during the infusion and at 30 (+/- 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• 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 (+/- 5) minutes after the infusion.

No steroid premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating investigator in consultation with the PI. The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

12.4 PATIENT 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.

12.5 BLINDING OF STUDY DRUG

Blinding methods will not be employed; PEGPH20 and other agents will be administered in an open-label fashion.

12.6 RECEIVING, STORAGE, DISPENSING AND RETURN

12.6.1 Receipt of Drug Supplies

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.

12.6.2 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/Roche and Halozyme 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.

12.6.3 Disposing 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.

12.7 Summary of Assessments

Table 15 Study Calendar

Procedure	Screening	Cycle 1			Pre-Surgery	Cycle 2					Cycle 3			End of Study[2]	Standard of Care Chemo-therapy[3]	End of Chemo-therapy	Post Study Follow up [4]- Every 3 months
	Day -36 to -23 [1]	Day -22	Day -15 ± 3d	Day -7 ± 3d	Day 0 ± 5d	Week 2 ± 3d	Week 3 ± 3d if >Grade 2 AE	Weeks 4 to 8 ± 3d	Weeks 4 to 8 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d	Weeks 8 to 12 ± 3d	Weeks 8 to 12 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d				
Consent	X																
Medical history	X																
PDA cytology/ pathology confirmation [5]	X																
Physical examination [6], vital signs	X	X	X	X	X	X	X	X		X	X		X		X	X	X

Procedure	Screening	Cycle 1			Pre-Surgery	Cycle 2					Cycle 3			End of Study[2]	Standard of Care Chemo-therapy[3]	End of Chemo-therapy	Post Study Follow up [4]- Every 3 months
	Day -36 to -23 [1]	Day -22	Day -15 ± 3d	Day -7 ± 3d	Day 0 ± 5d	Week 2 ± 3d	Week 3 ± 3d if >Grade 2 AE	Weeks 4 to 8 ± 3d	Weeks 4 to 8 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d	Weeks 8 to 12 ± 3d	Weeks 8 to 12 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d				
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	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X
ECG [7]	X		X		X			X			X			X	X		
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X

Procedure	Screening	Cycle 1			Pre-Surgery	Cycle 2					Cycle 3			End of Study[2]	Standard of Care Chemo-therapy[3]	End of Chemo-therapy	Post Study Follow up[4]- Every 3 months
	Day -36 to -23[1]	Day -22	Day -15 ± 3d	Day -7 ± 3d	Day 0 ± 5d	Week 2 ± 3d	Week 3 ± 3d if >Grade 2 AE	Weeks 4 to 8 ± 3d	Weeks 4 to 8 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d	Weeks 8 to 12 ± 3d	Weeks 8 to 12 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d				
Panel[8]						X	X										
PT/PTT	X				X	X										X	
Fresh tumor biopsy[9]	X																X
TSH, free T3 (or total T3), free T4, Cortisol[10]	X				X			X						X		X	X
Viral serology[11]	X													X			
C-reactive protein	X															X	

Procedure	Screening	Cycle 1			Pre-Surgery	Cycle 2					Cycle 3			End of Study[2]	Standard of Care Chemo-therapy[3]	End of Chemo-therapy	Post Study Follow up [4]- Every 3 months
	Day -36 to -23 [1]	Day -22	Day -15 ± 3d	Day -7 ± 3d	Day 0 ± 5d	Week 2 ± 3d	Week 3 ± 3d if >Grade 2 AE	Weeks 4 to 8 ± 3d	Weeks 4 to 8 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d	Weeks 8 to 12 ± 3d	Weeks 8 to 12 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d				
LDH	X													X			
CPK	X	X			X			X			X						
Ca 19-9 and CEA	X			X	X		X	X			X			X	X		
Pregnancy Test [12]	X	X			X			X					X	X		X	
Urinalysis	X	As clinically indicated														X	X
PBMC samples for biomarker		X			X			X			X	X		X	X		

Procedure	Screening	Cycle 1			Pre-Surgery	Cycle 2					Cycle 3			End of Study[2]	Standard of Care Chemo-therapy[3]	End of Chemo-therapy	Post Study Follow up [4]- Every 3 months
	Day -36 to -23 [1]	Day -22	Day -15 ± 3d	Day -7 ± 3d	Day 0 ± 5d	Week 2 ± 3d	Week 3 ± 3d if >Grade 2 AE	Weeks 4 to 8 ± 3d	Weeks 4 to 8 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d	Weeks 8 to 12 ± 3d	Weeks 8 to 12 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d				
Tumor response assessments [13]	X							X						X	X	X	X
Concomitant medications	X	X			X	X	X	X			X			X			
Adverse events	X	X	X	X	X	X	X	X		X	X		X		X	X	X
Atezolizumab administration [14]		X		X				X		X	X		X				
PEGPH20 administration		1[17],	3, 4	5, 6					7	8	9	10	11	12			

Procedure	Screening	Cycle 1			Pre-Surgery	Cycle 2					Cycle 3			End of Study[2]	Standard of Care Chemo-therapy[3]	End of Chemo-therapy	Post Study Follow up [4]- Every 3 months
	Day -36 to -23 [1]	Day -22	Day -15 ± 3d	Day -7 ± 3d	Day 0 ± 5d	Week 2 ± 3d	Week 3 ± 3d if >Grade 2 AE	Weeks 4 to 8 ± 3d	Weeks 4 to 8 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d	Weeks 8 to 12 ± 3d	Weeks 8 to 12 + 1w ± 3d	Weeks 4 to 8 + 2w ± 3d				
[15,17]		2[17]															
Intraoperative biopsy, surgery, dMMR/MSI[16]					X												
Survival follow-up [17]																	X
Cohort-specific assessment[18]	X																

CEA = carcinoembryonic antigen; CT = computed tomography; d = day; ECOG = Eastern Cooperative Oncology Group; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis B virus; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PDA = pancreas adenocarcinoma; TSH = Thyroid stimulating hormone; w = week.

[1] Protocol-specified screening procedures that are performed as part of standard of care and within 14 days of Day 1 of Cycle 1 may be used for screening purposes. Clinical laboratory studies and baseline CT and or MRI scan must be performed within the **7-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 visit should be scheduled within the 28-day period after the last dose of study drug, or 28 days after removal from study.

[3] Adjuvant modified FOLFIRINOX will be administered as described in Section 9.1.4.

[4] Patients will be seen every 3 months during years 1 through 3 (+/- 14 days) and every six months for years 4 and 5 (+/- 28 days) with blood work including CEA and Ca19-9 and imaging as per standard of care surveillance.

[5] Cytologic or histologic proof of PDA needs to be verified by the treating institution pathologist either on the initial diagnosis, or on the required pre-treatment biopsy. Pathological report from non-treating institutions is sufficient to consent if tissue sample is unavailable for evaluation at time of consent. However, in such a case, PDA diagnosis will need to be confirmed on the pre-treatment biopsy prior to initiation of treatment.

[6] A complete physical examination will be performed at screening. All subsequent physical examinations will be focused disease-specific exams. Subjects will be under go physical exams as indicated and every other week after surgery until initiation of cycle 2 or deemed not a candidate to receive therapy. Physical exam on week 3 after surgery is optional and dependent on clinical necessity.

[7] ECG recordings will be obtained during screening, prior to surgery, and during end-of-study. Patients should be resting in a supine position for at least 5 minutes prior to ECG recording.

[8] A 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 **weekly during the first cycle,** prior to surgery, weeks 2 and every other week after surgery until start of cycle 2 or until considered not eligible to initiate adjuvant CIT, week 3 after surgery if grade 3 or higher adverse events during week 2 visit except for pain and fatigue, and then on day 1 and 15 of cycle 2 and 3.Blood work prior to chemotherapy as standard of care will be obtained and comprehensive metabolic panel obtained as per institutional guidelines and as clinically indicated.

[9] Fresh tumor tissue samples will be collected from all patients by means of a biopsy performed at study entry. Adequate tissue collection to confirm diagnosis as deemed by the on-site pathologist on a preliminary review will be required for eligibility. If diagnosis is not confirmed, an attempt to repeat tumor biopsy is allowed if deemed safe, patient agreeable to repeat procedure, and performed at least 3 days prior to scheduled start of therapy. Optional tumor biopsy at time of recurrence (listed here as on follow-up).

[10] TSH, free T3 (or total T3 for sites where free T3 is not performed), free T4, and AM cortisol will be assessed at screening and on pre-surgery, Day 1 of Cycle 2, on end of study, and as clinically appropriate.

[11] 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.

[12] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to initiation of study treatment. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[13] All measurable and evaluable lesions should be assessed and documented at **screening (within 7 days of cycle 1 day 1)**, prior to start of investigational adjuvant therapy (**Day 1 of Cycle 2**;+/- 7 days), **prior to adjuvant chemotherapy** (+/- 7 days), during adjuvant **chemotherapy at every 8-week** interval (+/- 7 days), and **after adjuvant chemotherapy** at **every 12 week interval** (+/- 14 days). Tumor assessments performed as standard of care prior to obtaining informed consent and within **7 days** prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator s discretion, other methods of assessment of measurable disease as per imRECIST may be used. Refer to Section 13 for further details on tumor assessments.

[14] 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.

[15] All patients in Cohort 2 will receive PEGPH20 at a dose of 3□g/kg IV on Days 1 and 4 every week for 3 weeks **prior to** surgery and on Days 1, 8, and 15 on a 28 day cycle for 2 cycles **after** surgery. Patients are to receive Enoxaparin as detailed in the study protocol.

[16] At the time of surgery, four random core biopsies from the tumor will be obtained by the surgeon performing the PDA resection by direct visualization and cores processed if deemed safe. Standard of care microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) will be performed by the treating institution if not already performed.

[17] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[18] Following screening assessments need to be performed for specific cohorts

A. Atezolizumab in combination with PEGPH20

i. Doppler ultrasound of both legs will be performed during screening to exclude subjects with DVT and PE.

ii. 2cc plasma samples should be collected prior to PEGPH20 administration on C1D1 and C1D4 (2 hour window).

13. MEASUREMENT OF EFFECT

13.1 DEFINITION OF RESECTABLE DISEASE

Imaging Technique

All patients will undergo preoperative multiphasic CT (MDCT) scan for local staging using a dedicated pancreatic tumor imaging protocol. MRI of the abdomen may be used if unable to obtain contrasted CT scan or better definition for staging.

CT Protocol

The multiphasic CT (MDCT) pancreatic tumor protocol consists of three phases: pre-contrast, post-contrast pancreatic parenchymal phase (40-50 seconds after IV contrast injection) and post-contrast portal venous phase (65-70 seconds after IV contrast injection). The rate of IV contrast injection will be 4-5 mL/sec, iodine concentration = 300 mg/mL, and the volume of injected contrast will be based on patient s body weight (100 mL for patients weighing ≤ 250 lb and 150 mL for patients weighing >250 lb). In addition to IV contrast, enteric contrast will be administered. CT images will be acquired at slice thickness of ≤ 1 mm and reconstructed for axial sections (2-5 mm slice thickness) and multiplanar coronal and sagittal reformations (2-3 mm thickness).

MRI Protocol

Abdominal MRI without and with IV contrast will be performed if there is any contraindication to iodinated CT contrast, or for further assessment of the liver parenchyma, or better definition of staging. MRI pancreatic protocol includes T1 weighted imaging using in and opposed phase, axial and coronal T2 weighted, diffusion weighted, fat suppressed dynamic pre/post IV contrast gradient, echo T1 weighted imaging with slice thickness (interpolated to 2-3 mm), and heavily T2 weighted MRCP imaging in 2D and 3D.

Image Interpretation

Imaging will be interpreted by a designated radiologist as determined by the PI at the designated treating institution. Standard reporting of salient features will be performed as per consensus statement of the Society of Abdominal Radiology and American Pancreatic Association (Al-Hawary et al. 2014). The NCCN criteria for pancreatic cancer staging will be used for determining resectability in combination with institutional multidisciplinary pancreatic team assessment (Tempero et al. 2017).

Definition of Resectable Disease

Each patient CT or MRI scan will be reviewed by the treatment site designated radiologist to determine the respectability of the pancreatic tumor. ***A reconciliation conference will be held between the designated radiologists at each site if clear radiologic resectable disease cannot be determined to determine eligibility.*** If a consensus cannot be reached within 3 working days of the scan, the patient will be

deemed ineligible. Each evaluable patient will need a baseline image assessment form signed by the treatment site designated radiologist to deem eligibility for resectability (Appendix 1).

13.2 ANTITUMOR EFFECT – SOLID TUMORS

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

Treatment Beyond Initial Radiographic Recurrence

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-recurrence, this study will allow patients randomly assigned to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic recurrence per immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), provided the benefit-risk ratio is judged to be favorable by the investigator.

Patients should be discontinued for 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). Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudo-progression) with atezolizumab treatment, radiographic recurrence per RECIST v1.1 may not be indicative of true disease recurrence. In the absence of unacceptable toxicity, patients who meet criteria for disease recurrence per RECIST v1.1 while receiving treatment with atezolizumab or other treatments will be permitted to continue treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal 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.

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 within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al. 2009) in the same manner that immune- related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized Table 16.

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

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1), in the same manner that immune-related response criteria were adapted from WHO criteria and RECIST v1.0 (Ritchie et al. 2015; H nzelmann S et al. 2013). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 16.

Table 16 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	≥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.

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 for suspicion of recurrence.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride 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.

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.

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.

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

Chest CT 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.

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 and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

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.

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

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

ASSESSMENT OF TUMOR BURDEN

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

DEFINITION OF TARGET AND NON-TARGET LESIONS

Baseline scan should contain pancreas-specific mass to be considered eligible, and no measurable lesion considered concerning for metastatic disease. All measurable non-pancreatic lesions should be biopsied to confirm benign lesion.

Target lesions present at the time of recurrence should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected. ***If a new lesion is identified on first radiologic evaluation after PDA resection, a biopsy to confirm recurrence is required if deemed safe. However, if a biopsy is not feasible, treatment beyond progression is allowed.***

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 $\geq$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").

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.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions,

with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent 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.

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes 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).

<u>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 not be ticked.</u>

Measuring Lesions That Split or Coalesce on Treatment

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

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

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

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

DEFINITION OF RESPONSE CRITERIA

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

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

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

  New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or partial response (PR) nor sufficient increase to qualify for PD.

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 two 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.

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.

Stopping Rules

The study may be discontinued if the study is terminated by the data and safety monitoring committee, the FDA, or other regulatory authorities.

A safety committee of participating surgeons and medical oncologists at CUMC and Memorial Sloan Kettering Cancer Center will convene on a regularly scheduled basis to discuss study conduct. ***If greater than two of the 20 patients per cohort are unable to undergo surgery, or greater than four of the 20 patients per cohort have a greater than 14-day delay in surgery, deemed related to study treatment, enrollment to that arm will be halted and an analysis performed by the PI.*** The PI, in consultation with the safety committee, will either modify the treatment regimen or discontinue the arm if an alternate safe regimen is not deemed feasible.

Other Response Parameters

Exploratory endpoints will be evaluated on tissue samples obtained from core biopsies and resected tissue for co-immunofluoresence for immune markers, RNA-sequence analysis for expression profile within neoplastic epithelium and stroma, and other analysis. Please refer to the **laboratory manual** describing sample collection procedures.

14. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 11 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 14.3.

14.1 DATA COLLECTION

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.

14.2 DATA REPORTING

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

Serious Adverse Events that result in the patient not being able to undergo surgery, or result in a delay of surgery of greater than 14 days, as described in Section 5.1, are required to be entered in the Adverse Event Module in Velos within 24 hours of the event occurring/Investigator being aware of event.

14.3 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 patient 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 patients.

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 PI 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 the DSMC s conclusion with respect to progress or need for modification of the protocol.

14.4 QUALITY CONTROL AND QUALITY ASSURANCE

Independent monitoring of the clinical study for protocol and Good Clinical Practice (GCP) compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at CUMC may audit the study at any time per institutional policies and procedures. The investigator-Sponsor and CUMC 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 patient charts, and data elements to be monitored. 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.

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 visit and arrange for access to study materials and documentation.
- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first patient is enrolled 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 site s lead 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 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.

14.5 CONFIDENTIALITY

Information about study patients will be kept confidential and managed according to the requirements of the HIPAA. Those regulations require a signed patient authorization informing the patient of the following:

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

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients 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 patient is alive) at the end of their scheduled study period.

The patient 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.

14.6 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, patients 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, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.7 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 patients 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 two 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.

15. STATISTICAL CONSIDERATIONS

15.1 STUDY DESIGN/ENDPOINTS

This is a randomized phase 2 study with a biological endpoint aimed at comparing $CD8^+$ T-cell count within the resected tumor with neoadjuvant atezolizumab vs atezolizumab + PEGPH20 or other combinations at the time of surgery. All patients who meet inclusion/exclusion criteria and who receive 1 dose of study related treatment will be considered evaluable.

Primary Endpoint:

The primary endpoint is change in the number of intratumoral CD8+ T cells at time of surgery between treatment arm(s) compared to the atezolizumab arm.

Briefly, to obtain CD8+ T-cell count, we will probe formalin-fixed paraffin-embedded (FFPE) biopsy and resected tissue sections with distinct markers using quantitative multiplex immunofluorescence (qmIF)(Deng et al. 2016). This process involves a novel tyramide signal amplification (TSA) multiplexing technique that enables serial staining on the same section enabling simultaneous examination of up to eight epitopes. Multiple markers for distinct cell types will be used to investigate the tumor microenvironment. Some of these include, but are not limited to, pan T-cell (CD3), CD8+ T-cell (CD8), CD4+ T-cell (CD4), regulatory T-cell (FOXP3), PD-L1, myeloid (CD68), neoplastic (CK19), and nuclear (DAPI) markers. Images are visualized using Vectra microscope and analyzed using inForm Tissue Finder analysis software, which uses algorithms for machine learning based on cell morphology which includes membrane phenotype and cytoplasmic and nuclear stains, each cell is also assigned a coordinate on the slide for spacial analysis. This information is used to perform nearest neighbor analysis to

determine the location of cells relative to each other. Distance between immune subtypes and neoplastic cells will be analyzed to correlate with tumor cell death and clinical outcome. A designated gastrointestinal (GI) pathologist will review each hematoxylin and eosin (H&E) stained serial section and qmIF slide to oversee the process. Representative areas within the slide will be used for cell counts and nearest neighbor analysis. Simple immunohistochemistry (IHC) will be used in unforeseen circumstances where qmIF is not possible to quantitate CD8+ T cells.

Secondary Endpoint:

a) To estimate the 18-month survival rate and overall survival in patients treated with atezolizumab vs atezolizumab + PEGPH20 followed by surgery and adjuvant therapy.

b) To determine the R0 resection rates with atezolizumab vs atezolizumab + PEGPH20 administered in the neoadjuvant setting.

c) To determine the safety profile with atezolizumab vs atezolizumab + PEGPH20 followed by surgery and adjuvant therapy.

d) To evaluate Ca 19-9 biomarker responses to atezolizumab with or without PEGPH20 in the neoadjuvant setting.

e) To evaluate patterns of failure following neoadjuvant atezolizumab with or without PEGPH20 and surgery.

f) Intratumoral $CD8^+$ T cells after neoadjuvant atezolizumab alone or combination with PEGPH20 at time of surgery will be compared to intratumoral $CD8^+$ T cells within resected tumors after no neoadjuvant therapy from matched historical controls.

Exploratory Endpoints:

a) To isolate the epithelium and stromal tumor compartments for protein expression profiling using RNA-seq for subtype classification of PDA. This will be performed using LCM on resected tissue samples from patients treated with atezolizumab vs atezolizumab + PEGPH20.

b) To quantitate the change in $CD8^+$ T cells within paired pre-treatment biopsy and on-treated resected tumor treated with atezolizumab vs atezolizumab + PEGPH20.

c) To quantitate distinct immune subtypes within on-treatment tumor treated with atezolizumab vs atezolizumab + PEGPH20 by quantitative multiplex immunofluorescence.

d) To quantitate the change in immune subtypes within paired pre-treatment biopsy and on-treatment resected tumor treated with atezolizumab vs atezolizumab + PEGPH20.

Sample size justification:

For the primary endpoint of $CD8^+$ T-cell infiltration, a group sample size of 17 achieves at least 80% power to detect a difference of 1 SD with a significance level (alpha) of

0.05 using a two-sided two-sample t-test. Since PDA tumors contain sparse $CD8^+$ T cells, we expect that a two- fold increase in $CD8^+$ T- cell infiltration will have a clinically meaningful effect. From our experience, we estimate an attrition rate of 15% with inevaluable tissue; therefore, 20 patients per cohort will be recruited.

Study Arms:

Arm A. Atezolizumab alone
Arm B. Atezolizumab with PEGPH20

Additional arms will be added as deemed appropriate.

Patients will be randomly assigned to one of the study arms with an approximately equal ratio.

15.2 STRATIFICATION FACTORS

There are no stratification factors.

15.3 ANALYSIS OF PRIMARY, SECONDARY ENDPOINTS AND EVALUATION OF TISSUE

Primary Analysis:

The $CD8^+$ T-cell count within the tumor with neoadjuvant atezolizumab vs atezolizumab + PEGPH20 or other combinations at the time of surgery will be reported using means and standard deviations by group and will be compared using a two-sample T-test. If the data are not normally distributed, non-parametric models such as the Wilcoxon Rank Sum test will be used. Moreover, the distribution of $CD8^+$ T-cell count by treatment arm will be assessed using box plots, histograms, and q-q plots.

Secondary Analysis:

Overall survival (OS) and Recurrence-free survival

Overall survival and recurrence- free survival (RFS) will be estimated using the Kaplan Meier method. We will calculate and report the 18-months OS rate and the median OS/RFS along with their 95% confidence intervals. Kaplan Meier graphs will be done. OS and RFS will be compared by treatment arm using the log-rank test.

R0 Resection Rate

R0 resection rate is defined by the proportion of patients in whom an R0 resection was achieved during surgery which is defined by complete removal of macroscopic tumor which contains negative microscopic surgical margins. The R0 resection rate will be estimated by the number of patients in whom R0 resection was performed divided by total number of patients in each study arm. The R0 resection rate will be reported

along with the exact 95% confidence interval. We will compare the R0 resection rates using Fisher s exact test.

Safety:

The frequency and count of grade 3 or higher adverse events will be reported by treatment group. The maximum grade for each type of adverse events will also be reported. These will be reported over 4 periods:

a) Neoadjuvant Study Period

Defined as time of starting study-related therapy until induction of anesthesia prior to pancreas resection surgery.

b) Surgery Period

Surgical complications during time of surgery starting at time of induction of anesthesia for surgery until 90 days post- surgery or start of study-related adjuvant therapy, whichever is shorter.

c) Adjuvant Study Period

Defined as period from start of study-related adjuvant therapy until start of adjuvant chemotherapy.

d) Adjuvant Chemotherapy Period

Defined as period from start of adjuvant chemotherapy until 28 days after completing adjuvant therapy.

Exploratory Analysis:

Laser capture microdissection and RNA-Seq Analysis:

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 (Team 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 (H nzelmann et al. 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].

$CD8^+$ T cell infiltration:

Exploratory studies will measure $CD8^+$ T-cell numbers by immunohistochemistry (IHC) or qmIF performed to determine tumor-infiltrating lymphocyte infiltration from paired fresh tumor biopsies or resection samples, if available.

Change in $CD8^+$ T cells before and after treatment will be evaluated and compared using paired T-test by treatment. If the expression levels are not normally distributed, non-parametric methods such as the Wilcoxon Signed Rank test will be used. The change in $CD8^+$ T cells will also be compared by treatment using the two-sample T-test.

Immune subtypes:

Immune subtypes within the tumor with neoadjuvant atezolizumab vs atezolizumab + PEGPH20 or other combinations at the time of surgery will be reported using means and standard deviations by treatment group and will be compared using a two-sample T-test.

In addition, if adequate tissue sample is available, the change in immune subtypes before and after treatment will be evaluated and compared using paired T-test by treatment group. If the expression levels are not normally distributed, non-parametric methods such as the Wilcoxon Signed Rank test will be used.

15.4 REPORTING AND EXCLUSIONS

All patients who signed informed consent, and receive any protocol-defined treatment will be evaluable from the time of their first treatment with any study drug.

16. PROTECTION OF HUMAN PATIENTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures. An IND annual report will be submitted to the FDA in accordance with 21.CFR 312.33.

This protocol and any amendments will be submitted to a properly constituted 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 patients for this study will be provided a consent form describing this study and providing sufficient information for patients 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 for the study. The formal consent of a patient, using the IRB-approved consent form, must be obtained before that patient is submitted to

any study procedure. This consent form must be signed by the patient or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

17. STUDY FINANCES

Investigator initiated clinical trial is supported by Genentech/Roche.

17.1 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.

17.2 PATIENT STIPENDS OR PAYMENTS

There are no patient stipends or payments.

18. PUBLICATION PLAN

Neither the complete results 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. GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

19.1 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 adverse events and updates on unresolved adverse events and new safety information)

- Protocol violations
- Other issues affecting the conduct of the study

19.2 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.

19.3 REGULATORY DOCUMENTS

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 PI, 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 PI 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)

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 AAAS1908@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

19.4 SITE ACTIVATION

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

19.5 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 AAAS1908@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 at with a request to register the patient pending eligibility. The title of the email should read, AAAS1908 Pending Patient Registration Request (PHI) . The following documents should be submitted with the pending registration request, as applicable:
    a) Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b) Redacted Signed HIPAA (or institutional equivalent)
    c) 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:
    a) Notify of pending registration request
    b) Confirm method of registration request submission (email or fax)

c) 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) A signed Affiliate Site Eligibility Checklist (signed by the investigator)

   b) 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.)

   c) Please note: subject line of email or fax should include the following: AAAS1908 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 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 screenfail/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.

19.6 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.

19.7 GUIDELINES FOR AFFILIATE SITE MONITORING

On-Site MCT Monitoring:

1. 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 study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

2. 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.

3. 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 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 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.

4. 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.

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:

  a) Informed consent procedures

  b) Eligibility criteria

  c) Protocol specific treatment compliance

  d) Protocol specific toxicity/outcome documentation/compliance

  e) Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)

  f) Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, IND Safety Reports submissions, etc).

  g) Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)

  h) Pharmacy accountability records

i) Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)

- Affiliate site remote monitoring reports will be sent to the lead PI, 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.

19.8 ADVERSE EVENT REPORTING

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 adverse event 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 adverse events and to analyze the significance of the current event in light of the previous reports.

Sub-Site Serious Adverse Event 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 PI.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall PI 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 serious adverse event **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 adverse event. Report serious adverse events 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 (AAAS1908@lists.cumc.columbia.edu)

The participating investigator must provide follow-up information on the serious adverse event 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, and whether the patient **continued** or withdrew from study participation or 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.

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.

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.

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 PI will review all applicable IND Safety Reports and has the responsibly for forwarding 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.

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.

19.9 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 not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

19.10 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.

19.11 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.

19.12 RECORD KEEPING AND RECORD RETENTION

The PI 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.

Appendix 1
Radiographic Image Assessment - Baseline Review

CT/MRI RESULTS

Was a CT or MRI of the abdomen performed? ☐Yes ☐No

(If yes), Date of CT or MRI of abdomen *(mm/day/yyyy)* _____

(If yes), Primary tumor identified ☐Yes ☐No ☐Not evaluable

(If yes), Location of tumor ☐Head/Neck/Uncinate ☐Body/Tail

(If yes), primary tumor size

Dimension 1_____*(mm)* Dimension 2_____*(mm)*

CRITERIA FOR RESECTABLE DISEASE

- Tumor contact with aorta ☐Yes ☐No
- Tumor contact with celiac ☐Yes ☐No
- axis ☐Yes ☐No
- Tumor contact with superior mesenteric ☐Yes ☐No
- artery Tumor contact with common ☐Yes ☐No
  hepatic artery Tumor contact with
  - If yes →
    - tumor involvement >180 degrees ☐Yes ☐No
    - SMV contour irregularity or thrombosis ☐Yes ☐No
- Tumor contact with portal vein ☐Yes ☐No
  - If yes →
    - tumor involvement >180 degrees ☐Yes ☐No
    - If yes → PV contour irregularity or ☐Yes ☐No
- Tumor metastasis in chest, abdomen, or pelvis ☐Yes ☐No

RADIOGRAPHIC STAGE

Radiographic stage *(check one)*

☐**Resectable**
☐Non-resectable
☐Metastatic
☐Not evaluable

Treatment Site

☐ Columbia University
☐Memorial Sloan Kettering

Cancer Center Treatment Site Designated Radiologist Signature:

_____

Date of Review: _____

Appendix 2
Adverse Events and Management Guidelines for Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, 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 the investigator (or an appropriate delegate) from the study Principal Investigator.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Appendix 2: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL = bronchoscopic alveolar lavage.

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

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

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

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [1] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3]

LFT = liver function tests.

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

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

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

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [3] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function tests.

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

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

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

GASTROINTESTINAL EVENTS

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

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

Appendix 2: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

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

GI = gastrointestinal.

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

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

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

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [3] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

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

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

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

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and

magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. [3]

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

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [1] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. [3] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 2: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [1]. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3]
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab. [3] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

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

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

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

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an IRR with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue atezolizumab. [1]

IRR = infusion-related reaction.

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [1] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3] • For recurrent events, permanently discontinue atezolizumab. [3]

GI = gastrointestinal.

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

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

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

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [1] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3] • For recurrent events, permanently discontinue atezolizumab. [3]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [3] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

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

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

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

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [1] • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab. [3]

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

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

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

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barr syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [1] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [2] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [3]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [3] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barr syndrome (any grade)	• Permanently discontinue atezolizumab. [3] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

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

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

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

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

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

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

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

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

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

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

IMMUNE-RELATED MYOSITIS

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

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Related Myositis

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

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

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

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

Table 13 Management Guidelines for Immune-Related Myositis (cont.)

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

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

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

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

Appendix 2: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

SYSTEMIC IMMUNE ACTIVATION

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk for atezolizumab.

Recommendations regarding early identification and management of systemic immune activation are provided below. In the event of suspected systemic immune activation, atezolizumab should be withheld.

Early disease recognition is critical, and systemic immune activation should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge

  Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care

  Supplemental oxygen and intubation may be required.
- Fever $>38.5°C$
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, or coagulopathy

For patients with suspected systemic immune activation, an initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Soluble interleukin 2 (IL-2) receptor (soluble CD25)
- Triglycerides
- AST, ALT, and direct bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of systemic immune activation exists.

If neurologic abnormalities are present, consider cerebrospinal fluid analysis and/or an MRI of the brain.

If cytopenias are present (Grade ≥2 in two or more lineages) or ferritin is ≥3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Adenovirus, cytomegalovirus, Epstein-Barr virus, herpes-simplex virus, and human herpesvirus 6, 7, and 8 evaluations (for reactivated or active disease)

Diagnostic criteria and recommended management for systemic immune activation are provided in Table 14. The diagnostic criteria apply only when alternative etiologies have been excluded.

Appendix 2: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Table 14 Diagnostic Criteria and Recommended Management for Systemic Immune Activation

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
• Fever ≥ 38.5°C on more than one occasion • Ferritin ≥ 3000 ng/mL • Cytopenias (Grade ≥ 2 in two or more lineages) • Age-adjusted soluble interleukin-2 receptor elevated by ≥ 2 standard deviations • Severe (Grade ≥ 3) or progressive dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated γ-glutamyl transpeptidase (GGT) or liver function tests (AST, ALT, or direct bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥ 4 major criteria	Consistent with systemic immune activation	• Permanently discontinue atezolizumab. • Consider treatment with an immunosuppressive agent (i.e., cytokine inhibitors) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent, or dexamethasone ≥ 10 mg/m^2 once daily if neurologic abnormalities are present). • Consider HLH-2004 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable systemic immune activation	• Depending on clinical severity, follow guidelines for Consistent with systemic immune activation or Possible systemic immune activation diagnosis.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible systemic immune activation	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • Follow guidelines for Consistent with systemic immune activation diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the investigator.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).

Grades are based on National Cancer Institute Common Terminology Criteria for Adverse Events.

These recommendations do not replace clinical judgment and are intended as suggested guidance.

REFERENCES

Hejblum G, Lambotte O, Galicier L, et al. A web-based Delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. PLoS ONE 2014;9(4):e94024. doi: 10.1371/journal.pone.0094024

Appendix 3
Adverse Events and Management Guidelines for Atezolizumab + PEGPH20

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezolizumab + PEGPH20 Arm

Event	Action to Be Taken
IRRs and anaphylaxis	• Guidelines for management of IRRs for atezolizumab are provided in Appendix 2. • Guidelines for management of IRRs for PEGPH20 are provided below. • For anaphylaxis precautions, see Section 9.1.1.
IRR to PEGPH20, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR to PEGPH20, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRRs.
IRR to PEGPH20, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue treatment and contact the Principle Investigator.[1]

Atezo +PEGPH20 = atezolizumab plus PEGPH20; IRR = infusion-related reaction; MSE=musculoskeletal event; NSAID = nonsteroidal anti-inflammatory drug; OTC =over-the-counter; TE= thromboembolic.

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

Appendix 3: Guidelines for Management of Adverse Events Associated in Atezolizumab + PEGPH20 Arm

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezolizumab + PEGPH20 Arm (cont.)

Event	Action to Be Taken
Musculoskeletal event	
MSE, Grade 1	• Continue PEGPH20 and atezolizumab • Initiate prescription medications such as narcotics, muscle relaxants, NSAIDs or other analgesics (with the exception of steroids), OTC drugs, or physical therapy at the investigator s discretion.
MSE, Grade 2	• Withhold PEGPH20. Continue atezolizumab. • Initiate prescription medications such as narcotics, muscle relaxants, NSAIDs or other analgesics (with the exception of steroids), OTC drugs, or physical therapy at the investigator s discretion. • If event resolves to Grade 1 or better within 21 days, resume PEGPH20 at the current dose. If not, the Principal Investigator must be consulted to determine whether PEGPH20 should continue to be withheld, should be resumed at a lower dose (1.6 g/kg), or should be permanently discontinued.
MSE, Grade 3 or 4	• Withhold PEGPH20. Continue atezolizumab. • Initiate prescription medications such as narcotics, muscle relaxants, NSAIDs or other analgesics (with the exception of steroids), OTC drugs, or physical therapy at the investigator s discretion. • If event resolves to Grade 2 or better within 21 days and the Principal Investigator agrees that PEGPH20 should be continued, resume PEGPH20 at a lower dose (1.6 g/kg). If not, permanently discontinue PEGPH20.
Thromboembolic event	
TE event, Grade 1	• Continue PEGPH20 and atezolizumab.
TE event, Grade 2, 3, or 4	• Permanently discontinue PEGPH20. Withhold atezolizumab. • If patient becomes asymptomatic, resume atezolizumab. If not, permanently discontinue atezolizumab.

Atezo +PEGPH20 = atezolizumab plus PEGPH20; IRR = infusion-related reaction; MSE=musculoskeletal event; NSAID = nonsteroidal anti-inflammatory drug; OTC =over-the-counter; TE= thromboembolic.

Appendix 3: Guidelines for Management of Adverse Events Associated in Atezolizumab + PEGPH20 Arm

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezolizumab + PEGPH20 Arm (cont.)

Event	Action to Be Taken
Acute coronary syndrome, all grades	• Permanently discontinue PEGPH20. Withhold atezolizumab. • If patient becomes asymptomatic, resume atezolizumab. If not, permanently discontinue atezolizumab.
Stroke, all grades	• Permanently discontinue PEGPH20. Withhold atezolizumab. • If event resolves to Grade 1 or better, resume atezolizumab. If not, permanently discontinue atezolizumab.
Pulmonary events	
Pulmonary event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue PEGPH20. • For recurrent Grade 2 pneumonitis, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3	• Follow guidelines for atezolizumab in Appendix 2. • Withhold PEGPH20. • If event resolves to Grade 2 within 21 days and the Principal Investigator agrees that PEGPH20 should be continued, resume PEGPH20 at a lower dose (1.6 g/kg). • If event resolves to Grade 1 or better within 21 days, resume PEGPH20 at the current dose. • If event does not resolve to Grade 2 or better within 21 days, permanently discontinue PEGPH20.
Pulmonary event, Grade 4	• Follow guidelines for atezolizumab in Appendix 2. • Withhold PEGPH20. • If event resolves to Grade 2 or better within 21 days and the Principal Investigator that PEGPH20 should be continued, resume PEGPH20 at a lower dose (1.6 g/kg). If not, permanently discontinue PEGPH20.

Atezo +PEGPH20 = atezolizumab plus PEGPH20; IRR = infusion-related reaction; MSE=musculoskeletal event; NSAID = nonsteroidal anti-inflammatory drug; OTC =over-the-counter; TE= thromboembolic.

.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezolizumab + PEGPH20 Arm (cont.)

Event	Action to Be Taken
PEGPH20-related toxicities not described above	
Grade 1 or 2	• Continue PEGPH20 and atezolizumab.
Grade 3	• Withhold PEGPH20. Continue atezolizumab. • If event resolves to Grade 2 within 21 days and Principal Investigator agrees that PEGPH20 should be continued, resume PEGPH20 at a lower dose (1.6 g/kg). • If event resolves to Grade 1 or better within 21 days, resume PEGPH20 at the current dose. • If event does not resolve to Grade 2 or better within 21 days or Principal Investigator does not agree that PEGPH20 should be resumed, permanently discontinue PEGPH20.
Grade 4	• Withhold PEGPH20 and atezolizumab. • If event resolves to Grade 2 or better within 21 days and Principal Investigator agrees that PEGPH20 should be continued, resume PEGPH20 at a lower dose (1.6 g/kg). If not, permanently discontinue PEGPH20. • If event improves and the Principal Investigator agrees that atezolizumab should be continued, resume atezolizumab. If not, permanently discontinue atezolizumab.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 2. • Continue PEGPH20.
Grade 3	• Follow guidelines for atezolizumab in Appendix 2. • Withhold PEGPH20. • If event resolves to Grade 2 within 21 days and the Principal Investigator agrees that PEGPH20 should be continued, resume PEGPH20 at the current dose. • If event resolves to Grade 1 or better within 21 days, resume PEGPH20 at the current dose. • If event does not resolve to Grade 2 or better within 21 days or the Principal Investigator does not agree that PEGPH20 should be resumed, permanently discontinue PEGPH20.
Grade 4	• Follow guidelines for atezolizumab in Appendix 2. • Withhold PEGPH20. • If event resolves to Grade 2 or better within 21 days and the Principal Investigator agrees that PEGPH20 should be continued, resume PEGPH20 at the current dose. If not, permanently discontinue PEGPH20.

Atezo +PEGPH20 = atezolizumab plus PEGPH20; IRR = infusion-related reaction; MSE=musculoskeletal event; NSAID = nonsteroidal anti-inflammatory drug; OTC =over-the-counter; TE= thromboembolic.

20. REFERENCES

Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology. Jan 2014;270(1):248-260.

Allison DC, Piantadosi S, Hruban RH, et al. DNA content and other factors associated with ten-year survival after resection of pancreatic carcinoma. Journal of surgical oncology. Mar 1998;67(3):151-159.

Andre T, Vernerey D, Mineur L, et.al. J Clin Oncol. 2018 May 20;36(15):1469-1477. doi: 10.1200/JCO.2017.76.0355. Epub 2018 Apr 5.

Azuma K, Ota K, Kawahara A, et al. Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. Annals of oncology: official journal of the European Society for Medical Oncology. Oct 2014;25(10):1935- 1940.

Beatty GL, Torigian DA, Chiorean EG, et al. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clinical cancer research: an official journal of the American Association for Cancer Research. Nov 15 2013;19(22):6286-6295.

Boeck S, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta- analysis. Oncology. 2007;72(5-6):314-321.

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Jul 01 2010;28(19):3167-3175.

Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine. Jun 28 2012;366(26):2455-2465.

Carstens JL, Correa de Sampaio P, Yang D, et al. Spatial computation of intratumoral T cells correlates with survival of patients with pancreatic cancer. Nature communications. Apr 27 2017;8: 15095.

Chen N, Li Y, Ye Y, et al. Pharmacokinetics and pharmacodynamics of nab-paclitaxel in patients with solid tumors: disposition kinetics and pharmacology distinct from solvent-based paclitaxel. Journal of clinical pharmacology. Oct 2014;54(10):1097-1107.

Cheng XB, Sato N, Kohi S, et al. Prognostic impact of hyalouronan and its regulator in pancreatic ductal adenocarcinoma. PLoS One 2013;8: e80765.

Clark CE, Hingorani SR, Mick R, et al. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. Cancer research. Oct 01 2007;67(19):9518-9527.

Clift R, Lee J, Thompson CB, et al. PEGylated recombinant hyaluronidase PH20 (PEGPH20) enhances tumor infiltrating CD8+ T cell accumulation and improves checkpoint inhibitor efficacy in murine syngeneic breast cancer models [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017;77(13 Suppl): Abstract nr 641. doi:10.1158/1538-7445.AM2017-641.

Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. The New England journal of medicine. May 12 2011;364(19):1817- 1825.

Conroy T, Hammel P, Hebbar M, et al: Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine in patients with resected pancreatic ductal adenocarcinomas. 2018 ASCO Annual Meeting. Abstract LBA4001. Presented June 4, 2018.

D'Addio F, Riella LV, Mfarrej BG, et al. THE LINK BETWEEN PDL1 COSTIMULATORY PATHWAY AND TH17 IN FETOMATERNAL TOLERANCE. Journal of Immunology (Baltimore, Md.: 1950). 09/26 2011;187(9):4530-4541.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. mAbs. 2016;8(3):593-603.

Desai N, Trieu V, Yao Z, et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clinical cancer research: an official journal of the American Association for Cancer Research. Feb 15 2006;12(4):1317-1324.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). Jan 2009;45(2):228-247.

Ene-Obong A, Clear AJ, Watt J, et al. Activated Pancreatic Stellate Cells Sequester CD8(+) T-Cells to Reduce Their Infiltration of the Juxtatumoral Compartment of Pancreatic Ductal Adenocarcinoma. Gastroenterology. 07/25 2013;145(5):1121-1132.

Fukunaga A, Miyamoto M, Cho Y, et al. CD8+ tumor-infiltrating lymphocytes together with CD4+ tumor-infiltrating lymphocytes and dendritic cells improve the prognosis of patients with pancreatic adenocarcinoma. Pancreas. Jan 2004;28(1): e26-31.

Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. American journal of surgery. Jan 1993;165(1):68-72; discussion 72-63.

Guleria I, Khosroshahi A, Ansari MJ, et al. A critical role for the programmed death ligand 1 in fetomaternal tolerance. The Journal of experimental medicine. Jul 18 2005;202(2):231- 237.

Habicht A, Dada S, Jurewicz M, et al. A link between PDL1 and T regulatory cells in fetomaternal tolerance. J Immunol. Oct 15 2007;179(8):5211-5219.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Annals of oncology: official journal of the European Society for Medical Oncology. Oct 2010;21(10):1944-1951.

H nzelmann S, Castelo R, Guinney J. GSVA: gene set variation analysis for microarray and RNA-Seq data. BMC Bioinformatics. 2013 2013;14(1):1-15.

Hingorani SR, Zheng L, Bullock AJ, et al. HALO 202: Randomized Phase II Study of PEGPH20 Plus Nab-Paclitaxel/Gemcitabine Versus Nab-Paclitaxel/Gemcitabine in Patients With Untreated, Metastatic Pancreatic Ductal Adenocarcinoma.J Clin Oncol. 2018 Feb 1;36(4):359-366. doi: 10.1200/JCO.2017.74.9564. Epub 2017 Dec 12.

Hiraoka N, Onozato K, Kosuge T, et al. Prevalence of FOXP3+ regulatory T cells increases during the progression of pancreatic ductal adenocarcinoma and its premalignant lesions. Clinical cancer research: an official journal of the American Association for Cancer Research. Sep 15 2006;12(18):5423-5434.

Howard TJ, Krug JE, Yu J, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract. Dec 2006;10(10):1338-1345; discussion 1345-1336.

Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

Lee J, Leong M, Huang Y, et al. Combination of PEGylated recombinant hyaluronidase PH20 (PEGPH20) with live-attenuated, double-deleted (LADD) Listeria enhances tumor infiltrating CD8+ T cell response and antitumor efficacy in mice [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017;77(13 Suppl): Abstract nr LB-198. doi:10.1158/1538-7445.AM2017-LB-198.

Mahaseth HE, Brutcher J, Kauh N, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. 2013. Pancreas 42:1311 1315.

Marsh R, Talamonti M, Katz M, et al. Pancreatic cancer and FOLFIRINOX: a new era and new questions. 2015. Cancer Med 4(6): 853 863.

Metges JP, Ramee JF, Douillard JY, et al. Efficacy and safety of FOLFIRINOX in patients with metastatic pancreatic cancer. ASCO.2014. Meeting Abstr. 32(Suppl. 3): 305.

Moffitt RA, Marayati R, Flate EL, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. Oct 2015;47(10):1168-1178.

Mu CY, Huang JA, Chen Y, et al. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Medical oncology (Northwood, London, England). Sep 2011;28(3):682-688.

Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. The New England journal of medicine. Mar 18 2004;350(12):1200-1210.

Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. Jama. Sep 08 2010;304(10):1073-1081.

Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet (London, England). Mar 11 2017;389(10073):1011-1024.

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? Journal for immunotherapy of cancer. 2014;2: 17.

Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. Apr 01 2007;13(7):2151-2157.

Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Jama. Jan 17 2007;297(3):267-277.

Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. Jama. Oct 09 2013;310(14):1473-1481.

Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. International immunology. Jul 2007;19(7):813-824.

O'Reilly EM, Perelshteyn A, Jarnagin WR, et al. A single-arm, nonrandomized phase II trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma. Annals of surgery. Jul 2014;260(1):142-148.

Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 2012;21: 418 29.

Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer research. Jun 01 2014;74(11):2913- 2921.

Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of

pancreatic adenocarcinoma: a randomized controlled trial. Jama. Mar 05 2008;299(9):1019-1026.

Ritchie ME, Phipson B, Wu D, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015/4/20 2015;43(7): e47.

Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science (New York, N.Y.). Apr 03 2015;348(6230):124-128.

Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. Journal of immunotherapy (Hagerstown, Md.: 1997). Oct 2010;33(8):828-833.

Segal NH, Hamid O, Hwu W, et al. A phase I multi-arm dose-expansion study of the anti-programmed cell death-ligand-1 (PD-L1) antibody MEDI4736: Preliminary data. Ann Oncol. 2014;25(suppl 4): iv365.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. Jan-Feb 2016;66(1):7-30.

Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. The New England journal of medicine. Dec 04 2014;371(23):2189- 2199.

Soares KC, Rucki AA, Wu AA, et al. PD-1/PD-L1 blockade together with vaccine therapy facilitates effector T-cell infiltration into pancreatic tumors. Journal of immunotherapy (Hagerstown, Md.: 1997). Jan 2015;38(1):1-11.

Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract. Nov-Dec 2000;4(6):567-579.

Stein SM, James ES, Deng Y, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer. 2016 Mar 29;114(7):737-43

Stocken DD, Buchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. British journal of cancer. Apr 25 2005;92(8):1372- 1381.

Team RDC. R: A Language and Environment for Statistical Computing. Vienna, Austria 2016.

Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. Aug 2017;15(8):1028-1061.

Timmermann B, Kerick M, Roehr C, et al. Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. PloS one. Dec 22 2010;5(12): e15661.

Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Annals of surgery. Apr 1990;211(4):447-458.

Vincent A, Herman J, Schulick R, et al. Pancreatic cancer. Lancet (London, England). Aug 13 2011;378(9791):607-620.

Vonderheide RH, Bayne LJ. Inflammatory networks and immune surveillance of pancreatic carcinoma. Current opinion in immunology. 02/17 2013;25(2):200-205.

Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. The New England journal of medicine. Oct 31 2013;369(18):1691-1703.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research: an official journal of the American Association for Cancer Research. Dec 01 2009;15(23):7412-7420.

Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Annals of surgery. Oct 1995;222(4):580-588; discussion 588-592.