PROTOCOL	
TITLE:	**A PHASE I/II STUDY TO EVALUATE THE SAFETY, PHARMACODYNAMICS AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH ENTINOSTAT AND BEVACIZUMAB IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA**
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	Syndax
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PROTOCOL SIGNATURE PAGE

A Phase I/II study to evaluate the safety, pharmacodynamics and efficacy of atezolizumab in combination with entinostat and bevacizumab in patients with advanced renal cell carcinoma

VERSION DATE: June 8, 2023

I confirm 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 guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Indiana University Simon Comprehensive Cancer Center and keep a record for your files.

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Signature of Site Investigator Date

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Site Investigator Name (printed)

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
anti-HBc	antibody to hepatitis B core antigen
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
BSA	body surface area
CFR	Code of Federal Regulations

C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CNS	central nervous system
CL	clearance
CR	complete response
CRF	Case Report Form
CRO	contract research organization
CT	computed tomography
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
EC_{50}	50% effective concentrations
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	leucovorin, 5-fluorouracil, oxaliplatin
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
irAE	immune-related adverse event
IRB	Institutional Review Board
IRF	independent review facility

IRR	infusion-related reaction
irRC	immune-related response criteria
IV	intravenous
LFT	liver function test
LPLV	last patient, last visit
miRs	MicroRNA
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PES	polyethersulfone
PET	positron emission tomography
PFS	progression-free survival
PI	Package Insert
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
PUVA	psoralen plus ultraviolet A radiation
PVC	polyvinylchloride
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UBC	urothelial bladder cancer
ULN	upper limit of normal

V_{ss}	volume at steady state

1.0 INTRODUCTION

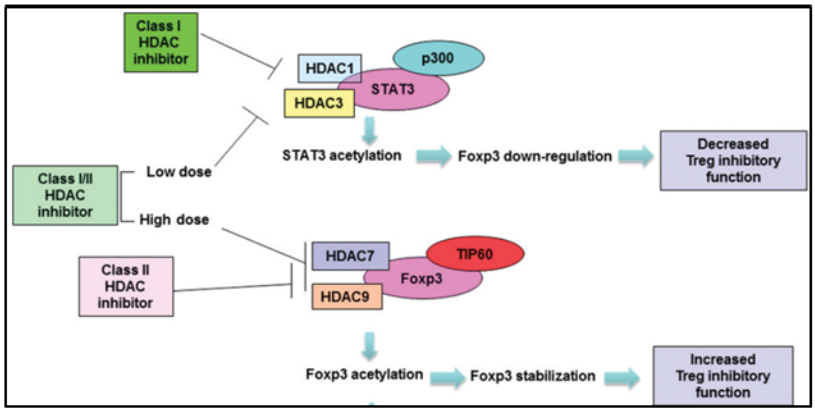
1.1 Renal cell carcinoma

Incidence of renal cell carcinoma (RCC) is reported 338,000 cases worldwide. RCC has a high mortality rate, causing an estimated 144,000 death each year.[1] Approximately 30% of patients are known to have metastatic disease at the time of diagnosis and another one third develop metastatic disease throughout their disease course.[2]

1.1.1 Current Management

Blocking the PD-1/PD-L1 interaction is a novel immunotherapeutic approach for the treatment of solid tumors including renal cell carcinoma (RCC). PD-1 inhibition has shown single-agent activity in clear cell RCC patients whose disease has progressed following VEGF pathway inhibitor therapy.[3] Though this new class of agents represents a very promising therapeutic strategy, only a fraction of patients seems to achieve durable responses.

Figure 1: Class I HDAC inhibition decreases Treg function and may enhance immune response. Class I HDAC inhibitors induce acetylation of STAT3 by inhibiting HDAC3 or HDAC1, down regulates Foxp3 gene expression and suppresses Treg function. Class II HDAC inhibitor treatment induces Foxp3 hyper acetylation by targeting HDAC7 and HDAC 9, which leads to stabilization of Foxp3 protein and enhanced Treg function. A pan inhibitor may target Class I HDACs at a low dose and impair Treg function. At a higher dose, the pan inhibitor may target also Class II HDAC and show a dominant Treg promoting effect (Shen L and Pili R Oncoimmunology 2013).



HDAC inhibitors induce acetylation of several histone and non-histone proteins, which contributes to a wide spectrum of anti-tumor and immunomodulatory activities of this class of agents. Pan HDAC inhibitors have shown either immunosuppressive or immunopromoting properties through modulating cytokine expression, affecting macrophage and dendritic cells, or regulating costimulation molecules. HDAC inhibitors have been also shown to induce activation of major histocompatibility complex (MHC) class I and class II proteins, and co-stimulatory molecules CD40, CD80 and CD86 (**Figure 1**).

The results from the clinical trials with HDAC inhibitors in cutaneous T-cell lymphoma and large cell lymphoma patients that have led to the approval of vorinostat and romidepsin suggest that the anti-tumor activity of these agents may be in part due to the modulation of the immune response. Our group has reported that the class I HDAC inhibitor, entinostat, suppresses regulatory T (Treg) cell function, enhances anti-tumor immune response and facilitates cytokine and vaccine immunotherapy in murine renal cell carcinoma and prostate cancer models, respectively.[4,5] This Treg suppression action does not seem to be through a depletion mechanism. On further analysis, we observed that entinostat suppresses Foxp3 gene expression in Treg cells and inhibits the suppressive function of Treg cells. Entinostat acetylates STAT 3 leading to down regulation of Foxp3. Our preclinical data

have shown the synergistic effect of entinostat in combination with high dose interleukin 2 (IL-2) in the RENCA model (*Kato Y et al, Clin Cancer Research 2008*). Based on our preclinical studies, we have initiated a Phase I/II clinical study with entinostat and high dose IL-2 in patients with metastatic renal cell carcinoma (*CTEP #7870*) (*Pili R et al ASCO GU 2016*). The primary objectives were to evaluate the safety, tolerability and efficacy of this combination strategy. The main eligibility criteria were clear cell histology, no prior treatments, and being fit to receive high dose IL-2. The Phase I portion consisted of two dose levels of entinostat (3 mg and 5 mg PO every 14 days) and a fixed standard dose of IL-2 (600,000 units/kg every 8 hours). To test our hypothesis, the fixed sample size at the Phase II dose level was 36 with a type I/II error of 10%. If 11 or more of the patients have a response, the hypothesis that the response rate of ≤ 20% is rejected. Dose levels 1 and 2 were completed without DLTs and 5 mg was the Recommended Phase II Dose for entinostat. The most common transient grade 3/4 toxicities were hypophosphatemia (16%), lymphopenia (15%), and hypocalcemia (7%). We have enrolled 47 patients (44 at dose level 2), and 37 have completed one cycle (84 days) of treatment. Four patients were not evaluable. Thirteen patients have achieved objective response (35%; 10 PR, 3 CR). To date, the median progression free survival (PFS) is 16.1 months. Decreased Tregs have been observed following treatment. Preliminary data suggest an association of higher activated antigen presenting cells and monocytic myeloid-derived suppressor cells (MDSCs) with objective responses. The preliminary results from this Phase I/II trial suggest that entinostat may increase the therapeutic effect of high dose IL-2 by modulating immunosuppressive cells.

Based on these data we have tested the effect of entinostat in combination with PD1 inhibition in a murine model of renal cell carcinoma (RENCA). As shown in **Figure 2**, entinostat enhanced the anti-tumor effect of an anti-PD1 antibody. These data suggest that HDAC inhibition may synergize with immune checkpoint inhibitors.

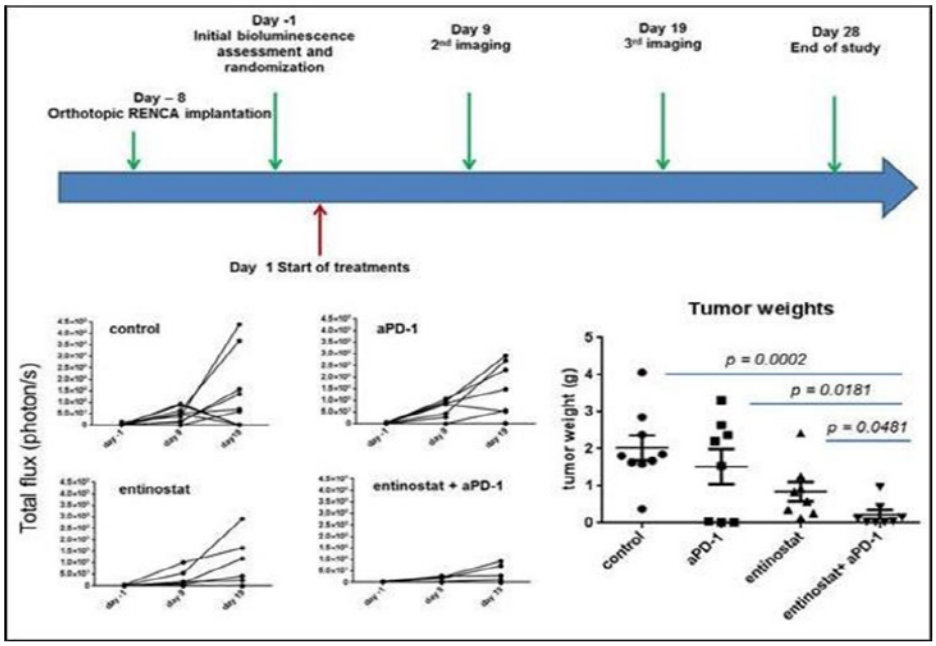


Figure 2: Entinostat enhances the anti-tumor effect of PD1 inhibition in the RENCA model. Murine renal cell carcinoma cells (RENCA) expressing luciferase were orthotopically implanted. Bioluminescence was assessed at regular intervals (see schema). Tumor bearing animals were randomized to either vehicle, anti-PD1, entinostat or combination. Endpoint tumor weights were collected on day 28.

1.1.2 Background on Atezolizumab

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. 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 human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (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. Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

1.1.3 Summary of Nonclinical Experience

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab.

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

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

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

1.1.4 Clinical Experience with Atezolizumab

1.1.4.1 Ongoing Clinical Studies

As of 17 May 2022, 122 studies are ongoing with atezolizumab as a single agent or in combination with other therapies. Of these, clinical data are available for more than 50 studies. Efficacy and/or safety data that are considered sufficiently robust and clinically relevant are available for more than 40 studies. Details of all ongoing studies can be found in the atezolizumab Investigator's Brochure.

1.1.4.2 Clinical Safety

As of 17 May 2022, an estimated total of >31,000 patients with solid tumor and hematologic malignancies have received atezolizumab in clinical trial participation as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy. Details regarding clinical safety can be found in the atezolizumab Investigator's Brochure.

1.1.4.2.1 Adverse Events

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, and no clear dose-related trends in the incidence of adverse events have been determined. Across all studies and tumor types, the most commonly reported adverse events with single-agent atezolizumab include fatigue, decreased appetite, nausea, cough, dyspnea, constipation, pyrexia, diarrhea, anemia, back pain, vomiting, asthenia, arthralgia, pruritus, rash, headache, urinary tract infection, and peripheral edema.

The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each 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.

1.1.4.2.2 Immune-Related Adverse Events

Immune-related adverse events 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 adverse events are closely monitored during the atezolizumab clinical program. As of this IB update, immune-related adverse events associated with atezolizumab include IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-related adverse events are described in further detail in Sections 6.4 and 6.5 of the atezolizumab Investigator's Brochure. Guidance regarding the management of immune-related adverse events is provided in Section 6.6 of the atezolizumab Investigator's Brochure.

1.1.4.3 Clinical Activity

1.1.4.3.1 Single-Agent All Indications

Study PCD4989g is an ongoing Phase Ia trial evaluating the safety and pharmacokinetics of single agent atezolizumab in patients with locally advanced or metastatic solid tumors or hematologic malignancies. As of the CCOD of 15 December 2015, safety information was available for 629 safety-evaluable patients from all lines of therapy, including for the following tumor types: NSCLC = 89, UC = 95, RCC = 72, TNBC = 111, and SCLC = 17. These safety-evaluable patients received a range of atezolizumab doses: ≤ 1 mg/kg q3w = 9, 3 mg/kg q3w = 3, 10 mg/kg q3w = 36, 15 mg/kg q3w = 236, 20 mg/kg q3w = 146, and 1200 mg q3w = 199. The median age of the 629 safety-evaluable patients was 61 years. This population was predominantly White (79.5%), approximately half were male (51.7% male vs. 48.3% female), and approximately half with an ECOG performance scores of 0 at baseline (45.2% with a performance score of 0 and 54.2% with a performance score of 1). Slightly more than half (53.7%) of the patients were current or previous smokers. This population represented all lines of therapy, with the vast majority of patients at 2L (30.8%) and 3L + (55.4%).

Overall, the safety profile of atezolizumab as monotherapy was generally consistent across the different indications. Please refer to the atezolizumab Investigator's Brochure for more detailed information.

1.1.4.3.2 Safety-Evaluable Renal Cell Carcinoma Patients

As of the CCOD of 15 December 2015, 72 safety-evaluable 1L + patients with RCC had received single-agent atezolizumab (3 mg/kg q3w = 2; 10 mg/kg q3w = 12; 15 mg/kg = 19; 20 mg/kg = 36; 1200 mg = 3). This population had a median age of 62 years.

Approximately three-quarters of the patients were white (75%) and male (76.4%). Slightly over half had an ECOG performance score of 0 at baseline (58.3%; the remainder had a baseline score of 1), and an equal number had never smoked (50%) versus those who were current smokers or with a prior history of smoking (50%).

Almost all the safety-evaluable patients (97.2%) with RCC reported one or more adverse events. The most common adverse events observed (≥ 20%) were fatigue (43.1%), cough (34.7%), arthralgia (30.6%), nausea and decreased appetite (27.8% each), constipation (26.4%), pyrexia (25.0%), back pain (23.6%), diarrhea and dyspnea (22.2% each), and anemia (20.8%).

Adverse events of Grade 3 or 4 severity were reported in 37 patients (51.4%), and in 13 (18.1%) patients, the events were considered related to atezolizumab by the investigator. The Grade 3−4 events that occurred in > 2 patients (> 2.8%) included dyspnea (9.7%), anemia (6.9%), and fatigue, asthenia, pleural effusion, pathological fracture, and hyperglycemia (4.2%). Most of the atezolizumab-related Grade 3−4 events were single occurrences, with fatigue and anemia reported in 4.2% or 3 patients each.

No safety-evaluable patient with RCC experienced a Grade 5 event (see Table 24).

Serious adverse events were observed in 27 patients (37.5%), with pyrexia and dyspnea (5.6% or 4 patients each) and pathological fracture and pleural effusion (4.2% or 3 patients each) being the most common. Of the 27 patients with serious adverse events, 8 (11.1%) had events that were assessed as related to atezolizumab. These events were pyrexia, influenza-like illness, ataxia, myasthenia gravis, autoimmune hypothyroidism, abdominal pain, suicide attempt, and dyspnea. All events but pyrexia (2 patients) were single occurrences.

The adverse events that led to atezolizumab discontinuation in 3 patients (4.2%) included a Grade 2 gaze palsy, a Grade 3 fatigue, and a Grade 4 suicide attempt.

Overall, the safety profile for this RCC cohort was consistent with the safety profile of atezolizumab for all safety-evaluable patients in Study PCD4989g, as well as with symptoms associated with the underlying disease.

Please refer to the atezolizumab Investigator's Brochure for further details.

1.1.4.3.3 Combination with Chemotherapy or Targeted Agents

Study GP28328 is an ongoing Phase Ib trial of atezolizumab in combination with bevacizumab and/or chemotherapy in patients with advanced solid tumors. As of the

CCOD of 14 January 2016, there were 208 safety-evaluable patients enrolled across six treatment arms:

- Arm A: atezolizumab + bevacizumab in patients with multiple solid tumor types including CRC and RCC (n = 64)
- Arm B: atezolizumab + bevacizumab + mFOLFOX-6 in patients with 1L CRC (n = 36)
- Arm C: atezolizumab + carboplatin + paclitaxel in patients with 1L NSCLC (n = 25)
- Arm D: atezolizumab + carboplatin + pemetrexed in patients with 1L NSCLC (n = 25)
- Arm E: atezolizumab + carboplatin + nab-paclitaxel in patients with 1L NSCLC (n = 26)
- Arm F: atezolizumab + nab-paclitaxel in patients with 1L +TNBC (n = 32)

Of the 208 safety-evaluable patients across all treatment arms, 99.5% reported an adverse event, with the most common (≥ 20%) being fatigue (63.0%), nausea (48.1%), diarrhea (44.2%), decreased appetite (33.2%), neutropenia (32.7%), constipation (29.8%), pyrexia (27.9%), vomiting (27.4%), neuropathy peripheral (26.9%), cough (25.0%), anemia (24.5%), arthralgia (24.0%), headache (21.6%), and alopecia (21.2%).

Grade 3−4 adverse events were reported in 70.7% of the safety-evaluable patients. The Grade 3−4 adverse events with the highest occurrences (≥ 10 patients or ≥ 4.8%) were neutropenia (26.0%), anemia (10.6%), diarrhea (5.8%), neutrophil count decreased (7.2%), pneumonia (5.3%), and thrombocytopenia and fatigue (4.8% each). The most common (≥ 5 patients or 2.4%) Grade 3−4 events related to atezolizumab as assessed by the investigator included neutropenia and fatigue (3.8% each) and anemia and AST increased (2.4% each).

Two patients (1.0%) experienced Grade 5 adverse events ≤ 30 days of discontinuing study treatment. Both were patients with NSCLC (Arms C and E), and the two events were pneumonia and systemic candida and were considered related to atezolizumab by the investigator. Two other patients experienced Grade 5 events > 30 days after discontinuation of study treatment that were assessed by the investigator as related to atezolizumab; an Arm C (NSCLC) patient with pneumonitis (with possible concurrent infectious source) and an Arm E (NSCLC) patient with autoimmune hepatitis (see also discussion on Arms C, D, and E below).

Serious adverse events were reported in 89 patients (42.8%). The events occurring in ≥ 5 patients or ≥ 2.4% of patients included pneumonia (5.3%), dehydration (3.4%), and pyrexia (2.9%), and febrile neutropenia and neutropenia (2.4% each). Serious adverse events considered related to atezolizumab included fatigue in 3 patients (1.4%) and pyrexia, febrile neutropenia, pneumonitis, and dehydration in 2 patients each (1.0%).

Overall, 12 patients (5.8%) discontinued atezolizumab due to adverse events regardless of causality. All events were single occurrences, with 8 patients reporting Grade 3 events (including decreased appetite, dehydration, hypercalcemia, platelet count decreased, hypoxia, and pneumonitis). The Grade 4 events were reported in 2 patients and were ALT and AST increased, neutropenia, and pancytopenia.

The safety profiles of the six treatment arms were generally comparable with each other, although Arm A, which is atezolizumab in combination with another monoclonal antibody versus a chemotherapeutic agent, had lower frequencies of Grade 3−4 events and related Grade 3−4 events. These safety data suggest that atezolizumab can be safely combined with standard chemotherapy treatments. Atezolizumab in combination with cytotoxic chemotherapy has not been associated with additive severe (Grade 3 or higher) toxicities. The adverse events observed for atezolizumab in combination with chemotherapy are consistent with the known risks of each study treatment.

Please refer to the atezolizumab Investigator's Brochure for more detailed information.

1.1.4.4 Clinical Pharmacokinetics and Immunogenicity

There have been no dedicated clinical pharmacology studies conducted for atezolizumab. Atezolizumab pharmacokinetics and other data have been analyzed from the following atezolizumab monotherapy studies: PCD4989g, JO28944, IMvigor 210, BIRCH, POPLAR, and FIR. No final PK data are available from studies where atezolizumab has been dosed in combination with other anti-cancer agents.

The pharmacokinetics of atezolizumab monotherapy have been characterized in patients in Study PCD4989g at doses 0.01 mg/kg to 20 mg/kg q3w, including the fixed dose 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of ATA-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab q3w experienced a reduction of atezolizumab C_{min} to below the PK assay lower limit of quantification (LOQ), patients receiving 10 to 20 mg/ kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the LOQ and the target serum concentration of 6 µg/mL (Deng et al. 2016).

A Phase I popPK analysis that included 472 patients from Studies PCD4989g and JO28944 described atezolizumab pharmacokinetics for the dose range 1-20 mg/kg with a linear two-compartment disposition model with first-order elimination. The popPK analysis indicated that central compartment volume of distribution (V1) was 3.28 L and the V_{ss} was 6.91 L in the typical patient. Further, the CL of atezolizumab was 0.20 L/day and the $t_{1/2}$ was 27 days. Steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in AUC, C_{max}, and C_{min} was 1.91, 1.46, and 2.75-fold, respectively.

Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21-89 years), body weight, gender, positive ATA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

The effect of moderate or severe hepatic impairment (bilirubin > ULN and AST > ULN or bilirubin 1.0 to 1.5 ≥ x ULN and any AST elevation) on the pharmacokinetics of atezolizumab is unknown.

1.1.4.5 Drug Interactions

No formal PK drug-drug interaction studies for atezolizumab have been conducted. There are no known interactions with other medicinal products or other form of interactions.

1.1.5 Marketing Experience

Atezolizumab was approved by the U.S. FDA in May 2016 for the treatment of patients with locally advanced or metastatic UC. Since 2016 it has been FDA approved for extensive-stage small cell lung cancer, hepatocellular carcinoma, and melanoma.

Additionally, atezolizumab for the treatment of locally advanced or metastatic UC and locally advanced or metastatic NSCLC is undergoing regulatory review in Europe and other countries.

1.2 Entinostat

1.2.1 Background

Entinostat is a member of the substituted pyridylcarbamate class of HDAC-inhibiting compounds with oral bioavailability (Saito 1999, Suzuki 1999). It selectively inhibits class I and IV HDACs, specifically, HDACs 1, 2, 3, and 11, thus promoting hyperacetylation of histones and allowing transcriptional activation of a distinct set of genes, ultimately inhibiting cell proliferation, terminal differentiation, and/or induced apoptosis. This isoform selectivity may differentiate the safety and efficacy profiles from those of nonselective pan-HDAC inhibitors.

Entinostat inhibits HDACs in vitro and has tumor cell growth-inhibiting activity in culture and in murine human xenograft models (Suzuki 1999, Saito 1999). Entinostat synergizes with and enhances the activity of a broad spectrum of anticancer agents. It also restores sensitivity to several anticancer agents in drug resistance models. Combinations with anti-estrogens, EGFRi, and DNMT inhibitors (DNMTi) are among the most promising to date.

Entinostat has been evaluated in >900 cancer patients with solid tumors (such as breast cancer and non-small cell lung cancer [NSCLC]) and numerous hematologic malignancies, as enumerated in Sections 1 and 5.2. In Phase 1 and Phase 2 studies, entinostat has been studied as a monotherapy and in combination with AIs, various kinase inhibitors, AZA, 13-cis-retinoic acid, and GM-CSF. Entinostat is currently in Phase 3 development.

Entinostat has been shown to induce acetylation and alter the function of multiple cancer relevant protein substrates. These cellular changes have provided the rationale for testing of entinostat in vitro and in vivo in combination with a wide range of targeted therapies, chemotherapies, and other epigenetic therapies (e.g., a DNMTi).

In studies reported to date, the pharmacokinetics of entinostat were linear over the dosages of 2 to 12 mg/m2 and were variable, with coefficients of variation (CV%) of approximately 40%. The terminal half-life of approximately 100 hours allows weekly or every-2-week dosing. Fixed dosing, was supported by analysis of covariates (e.g., body surface area [BSA], body-mass index [BMI], lean-body mass) in 64 patients (Acharya 2006). Histone

hyperacetylation was evident at all doses tested to date, confirming the intended pharmacologic effect.

Based on the results of the clinical studies, the recommended dose regimens for further development are 5 mg weekly, 10 mg every 2 weeks, or 7 mg weekly for 3 weeks of a 4-week cycle. Entinostat is to be administered on an empty stomach, at least 2 hours after a meal and 1 hour before the next meal. These recommendations are based on results from Phase 1 and 2 studies in which various doses (ranging from 1.7 to 17 mg/week) and regimens were evaluated. All doses tested showed evidence of histone hyperacetylation in PBMCs. A dose intensity of 20 mg every 4 weeks, which was generally tolerated well in the Phase 1 and 2 studies, is expected to be pharmacologically active and tolerable when given either alone or in combination with other anticancer treatments. This dose intensity can be achieved by dosing according to the regimens above. Entinostat has not yet been evaluated in pediatric populations.

For further details, see the entinostat Investigator's Brochure.

1.2.2 Safety Profile

The safety and efficacy of entinostat have been evaluated in >900 patients with cancer in 29 industry/NCI-sponsored clinical studies, of which 6 are ongoing. Regardless of indication and regimen, the most frequently reported AEs with entinostat included fatigue; GI disturbances, primarily nausea with or without vomiting, anorexia, and diarrhea; and hematologic abnormalities, primarily anemia, thrombocytopenia, neutropenia, and leukopenia. Grade 3 and 4 hematologic abnormalities were commonly seen in patients with hematologic malignancies, but were much less prevalent in patients with solid tumors.

Entinostat has been administered in combination with established anticancer agents in 22 clinical studies, 17 in patients with solid tumors and 5 in patients with hematologic malignancies. To date, a total of 699 patients have received at least 1 dose of entinostat in combination with another agent, including 494 patients with solid tumors and 205 patients with hematologic malignancies. Agents administered in combination with entinostat have included the AIs exemestane, letrozole, and anastrozole (n=111); erlotinib (n=99); AZA (n=319); and other agents (n=170).

Overall, 97% of the 699 patients who received entinostat in combination with another agent experienced at least 1 TEAE, including 96% of the 494 patients with solid tumors and all (100%) 205 patients with hematologic malignancies. In general, the most frequently reported AEs among patients receiving entinostat in combination, regardless of indication, were fatigue, nausea, anemia, thrombocytopenia, leukopenia, diarrhea, vomiting, and neutropenia.

In general, patients with hematologic malignancies tended to have a higher incidence of AEs, particularly hematologic toxicities. For instance, febrile neutropenia occurred at an incidence of 34% in patients with hematologic toxicities versus <1% in patients with solid tumors. However, difficulties arise in interpreting differences in AE incidences between the patient groups, as the differences may be influenced by the particular combination drug, the underlying malignancy, the stage of disease, the extent of prior treatment, and other baseline characteristics of the various populations.

For further details, see the entinostat Investigator's Brochure.

1.3 Bevacizumab

1.3.1 Background

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 22,000 patients and in multiple tumor types. Approximately 1,720, 000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.66 ($p < 0.001$) and a median survival of 20.3 vs. 15.6 months. Similar increases were seen in progression-free survival (10.6 vs. 6.2 months; HR 0.54, $p < 0.001$), overall response rate (34.8% vs. 44.8%; $p = 0.004$) and duration of response (10.4 vs. 7.1 months; HR 0.62, $p = 0.001$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, November 2012). Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU – based chemotherapy for subjects with metastatic colorectal cancer.

Bevacizumab has also been approved based on additional Phase III trials in metastatic CRC (E3200 and ML18147) non-small cell lung cancer (NSCLC; E4599), and renal cell carcinoma (RCC; AVOREN) which also demonstrated clinical benefit from bevacizumab. Furthermore, Phase II studies in glioblastoma (GBM; AVF3708g and NCI-06-C0064) showed an improvement in objective response rate. These studies led to accelerated approval by the FDA for recurrent GBM.

In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated, Bevacizumab naive metastatic CRC patients. In Study ML18147, bevacizumab in combination with oxaliplatin- or irinotecan-based chemotherapy regimens demonstrated a statistically significant increase in OS compared to oxaliplatin- or irinotecan-based chemotherapy alone (11.2 vs. 9.8 months, respectively, HR = 0.81; $p=0.0062$) in metastatic CRC patients who had previously received bevacizumab as a part of their 1st line treatment (Bennouna et al. 2013). These two studies led to FDA approvals for bevacizumab for previously treated metastatic CRC patients, in 2006 and 2013, respectively.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006.

In previously untreated metastatic RCC patients, bevacizumab in combination with interferon-alfa showed an improved progression free survival compared to interferon-alfa alone (10.2 vs. 5.4 months, respectively; HR=0.63; p=0.0001). These results supported the FDA approval of bevacizumab with interferon-alfa in metastatic RCC in July 2009.

Two Phase II trials investigated bevacizumab as a single agent in patients with recurrent GBM. In AVF3708g, patients with recurrent GBM were randomized to bevacizumab or bevacizumab plus irinotecan and demonstrated an improvement in objective response rate (28.2% vs. 37.8%, respectively). The NCI-06-C0064 study was single arm Phase II study in recurrent GBM patients treated with bevacizumab alone and showed an objective response rate of 19.6%. This study supported the results from AVF3708g, and based on the objective response rate in these two trials, the FDA granted accelerated approval for bevacizumab as a single agent in GBM patients with progressive disease following prior therapy. In 2013, results from two phase III randomized controlled trials for newly diagnosed GBM were presented, one Roche-sponsored trial (AVAglio) and one cooperative group trial (RTOG 0825). In AVAglio, progression free survival was significantly longer with bevacizumab when added to radiation therapy/temozolomide (HR 0.64, mPFS 10.6 vs 6.2 months). Health-related quality of life (HRQoL) and Karnofsky performance score (KPS) were stable/improved during PFS (both arms). Patients receiving bevacizumab plus radiation therapy/temozolomide had diminished corticosteroid requirement, but reported more adverse events (AEs) compared with placebo plus radiation therapy/temozolomide (serious AEs: 36.6% vs 25.7%; grade ≥3: 62.7% vs 50.1%; grade ≥3 AEs of special interest to bevacizumab: 28.7% vs 15.2%). In RTOG 0825, PFS was extended for bevacizumab (7.3 vs.10.7 months, HR 0.79) but did not meet the prespecified endpoint for significance. There was no difference between arms for overall survival (median 16.1 vs.15.7 months, HR 1.13).

Lastly, in the E2100 study, patients with untreated metastatic breast cancer who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively, HR 0.48; p<0.0001) and this led to the accelerated approval of bevacizumab in metastatic breast cancer. Unfortunately, the clinical benefit was not confirmed in subsequent trials and the FDA ultimately removed the label for the breast cancer indication. (See the Bevacizumab Investigator Brochure for additional details).

For further details, see the bevacizumab Investigator's Brochure.

1.3.2 Safety Profile

Hypertension: An increased incidence of hypertension (all grades) of up to 42.1% has been observed in patients treated with bevacizumab compared to up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of bevacizumab-treated patients, compared to up to 0.2% of patients treated with the same chemotherapy alone. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Analyses of the clinical safety data suggest that the occurrence of hypertension with Bevacizumab therapy is likely to be dose-dependent. Monitor blood pressure every two to

three weeks during treatment with bevacizumab. Treat with appropriate anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with bevacizumab -induced or -exacerbated hypertension after discontinuation of bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. In the event of Grade 4 proteinuria Bevacizumab treatment should be permanently discontinued. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy.

Analyses of the clinical safety data suggest that the occurrence of proteinuria with Bevacizumab therapy is likely to be dose-dependent. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical studies urine protein levels of ≥2g/24h led to the holding of bevacizumab until recovery to <2g/24h.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis: Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Bevacizumab treatment. In clinical trials across all indications the overall incidence of VTE events was 2.8%−17.3% in the bevacizumab-containing arms compared with 3.2%−15.6% in the chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive bevacizumab in combination with chemotherapy versus chemotherapy alone.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

In clinical trial BO21990, Grade 3-5 venous thromboembolic events were observed in 7.6% of patients with newly diagnosed glioblastoma treated with Bevacizumab in combination

with chemotherapy and radiotherapy, compared to 8.0 % of patients treated with chemotherapy and radiotherapy alone.

Bevacizumab should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events ≤Grade 3 need to be closely monitored.

Arterial Thromboembolism: An increased incidence of ATE events was observed in patients treated with bevacizumab across indications including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic events. Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab- containing arms compared up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of bevacizumab treated patients versus 0.5% of patients in the control group: myocardial infarction was reported in 1.4% of bevacizumab treated versus 0.7% of patients in the observed control group.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of bevacizumab patients compared to 5.8% (6/104) in the chemotherapy control group. In an uncontrolled clinical trial, AVF3708g, in patients with relapsed glioblastoma, arterial thromboembolic events were observed in 6.3% (5/79) of patients who received Bevacizumab in combination with irinotecan compared to 4.8% (4/84) of patients who received Bevacizumab alone.

Patients receiving Bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during Bevacizumab therapy. Caution should be taken when treating such patients with Bevacizumab.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005).

Gastrointestinal perforation: Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of <1% in patients with metastatic breast cancer or non-squamous NSCLC, up to 2% in metastatic renal cell cancer, newly diagnosed glioblastoma, or in patients with ovarian cancer receiving front-line treatment, and up to 2.7% (including

gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2-1% of all bevacizumab treated patients.

In Bevacizumab clinical trials, gastrointestinal fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations, including gastrointestinal fistulae and abscess (all grade) were reported in 10.1% of Bevacizumab treated patients, all of whom had a history of prior pelvic radiation. Fatal outcome was reported in 0.9% of Bevacizumab-treated patients. Most patients reported as having GI perforations in this study (15 out of 22) had GI-vaginal fistulae.

The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal x-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established.

Patients may be at increased risk for the development of gastrointestinal perforation and gallbladder perforation when treated with Bevacizumab. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), 4.1% of bevacizumab-treated patients and 2.3% of control patients were reported to have had vaginal, vesical or female genital tract fistulae (all grade), some of which were GI vaginal fistulae. The overall rate of GI-vaginal fistulae (all grade), combining both those reported as GI perforations and those reported as fistulae and abscess (as stated above) was 8.2% in bevacizumab-treated patients and 0.9% in control patients. Uncommon (≥0.1% to <1%) reports of other types of fistulae that involve areas of the body other than the gastrointestinal tract (e.g., bronchopleural, urogenital, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience. Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Non-Gastrointestinal Fistulae: Patients may be at increased risk for the development of fistulae when treated with bevacizumab.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported.

Necrotizing fasciitis including fatal cases, has rarely been reported in patients treated with Bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting bevacizumab treatment were excluded from participation in Phase III trials.

Across mCRC clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications occurring within 60 days of major surgery was observed if the patient was being treated with bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

In locally recurrent and metastatic breast and ovarian cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving bevacizumab compared with up to 0.9 % of patients in the control arms.

In the study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single- agent bevacizumab and 1.3% in patients treated with bevacizumab plus irinotecan.

In patients with newly diagnosed glioblastoma (study BO21990) the incidence of Grade 3-5 post-operative wound healing complications (including complications following craniotomy) was 3.3% when treated with Bevacizumab in combination with chemotherapy and radiotherapy, compared with 1.6 % when treated with chemotherapy and radiotherapy alone.

Bevacizumab should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. In patients who experience wound healing complications during Bevacizumab treatment, Bevacizumab should be withheld until the wound is fully healed. Bevacizumab therapy should be withheld for elective surgery. The appropriate interval between the last dose of bevacizumab and elective surgery is unknown; however, the half-life of bevacizumab is estimated to be 20 days. Suspend bevacizumab for at least 28 days prior to elective surgery. Do no administer bevacizumab until the wound is fully healed.

Hemorrhage: In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in bevacizumab-treated patients, compared to 0 to 4.5% of patients in the chemotherapy control group. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor- associated hemorrhage (see below) and minor mucocutaneous hemorrhage (e.g., epistaxis). Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during Bevacizumab therapy.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Possible risk factors include squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs,

treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location and cavitation of tumors prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumor histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade events were seen with a frequency of up to 9% when treated with bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Major or massive pulmonary hemorrhage/hemoptysis can occur suddenly and up to two thirds of the serious pulmonary hemorrhages resulted in a fatal outcome.

Patients with non–small cell lung cancer treated with Bevacizumab may be at risk for serious, and in some cases fatal, pulmonary hemorrhage/hemoptysis. Patients with recent pulmonary hemorrhage/ hemoptysis (>1/2 teaspoon red blood) should not be treated with Bevacizumab.

Pulmonary Hemorrhage/Hemoptysis: Patients with non–small cell lung cancer treated with bevacizumab may be at risk for serious, and in some cases fatal; pulmonary hemorrhage/hemoptysis. Patients with recent pulmonary hemorrhage/ hemoptysis (>1/2 teaspoon red blood) should not be treated with bevacizumab.

Mucocutaneus Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous hemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Posterior Reversible Encephalopathy Syndrome (PRES): PRES is a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of PRES. Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

In patients who develop PRES, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known (Glusker et al. 2006; Ozcan et al. 2006).

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In five Phase

III studies (AVF2119g, E2100, BO17708, AVF3694g and AVF3693g) in patients with metastatic breast cancer, Grade ≥ 3 CHF was reported in up to 3.5% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of Grade ≥ 3 CHF for the respective bevacizumab and control arms were similar to those in the other studies in mBC: 2.9% in the anthracycline+Bv arm and 0% in the anthracycline+placebo arm. In addition, in study AVF3694g the incidence of any grade CHF was similar between the anthracycline+Bv (6.2%) and the anthracycline+placebo arms (6.0%). Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of bevacizumab, patients with pre-existing CHF of NYHA II – IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma (BO20603) when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF in both arms was above that previously observed for doxorubicin therapy the rate was higher in the R-CHOP plus bevacizumab arm.

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with bevacizumab. Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

Ovarian Failure/Fertility: The incidence of new cases of ovarian failure, defined as amenorrhea lasting 3 or more months, FSH level ≥ 30mIU/ml and a negative serum β-HCG pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of women. Long term effects of treatment with bevacizumab on fertility are unknown.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Bevacizumab in comparison to chemotherapy alone.

Hypersensitivity reactions, infusion reactions: Patients may be at risk of developing infusion / hypersensitivity reactions. Close observation of the patient during and following

the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Bevacizumab in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of Bevacizumab is common (up to 5% in bevacizumab-treated patients).

Laboratory Abnormalities: Decreased neutrophil count, decreased white blood count and presence of urine protein may be associated with bevacizumab treatment. Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycemia, decreased hemoglobin, hypokalemia, hyponatremia, decreased white blood cell count, increased PT (prothrombin time), normalized ratio.

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

1.4 Study Rationale

This study will assess the immunomodulatory activity of entinostat in patients receiving the PD-L1 inhibitor atezolizumab. The overall hypothesis is that entinostat will increase the immune response and anti-tumor effect induced by the PD-L1 inhibition by suppressing Treg function. We have chosen renal cell carcinoma that has been reported to respond to PD1/PD-L 1 inhibition. The schedule of entinostat is based on our previous experience with this agent. Based on our working hypothesis that low dose HDAC inhibitors will have a suppressive function on Tregs but not on T effector cells, the starting dose of entinostat will be 1 mg and will be escalated up to 5 mg rather than the 10 mg dose. The combination also with bevacizumab will provide an effective VEGF inhibition that may potentiate the immune response and anti-tumor effect induced by atezolizumab.

2.0 Objectives

2.1 Primary

Phase I: To assess the safety and tolerability of atezolizumab in combination with entinostat and bevacizumab in patients with advanced renal cell carcinoma.

Phase II: To assess the objective response rate of atezolizumab in combination with entinostat and bevacizumab in anti-PD 1 naïve patients and atezolizumab in combination with entinostat in anti-PD 1 resistant patients with advanced renal cell carcinoma.

2.2 Secondary

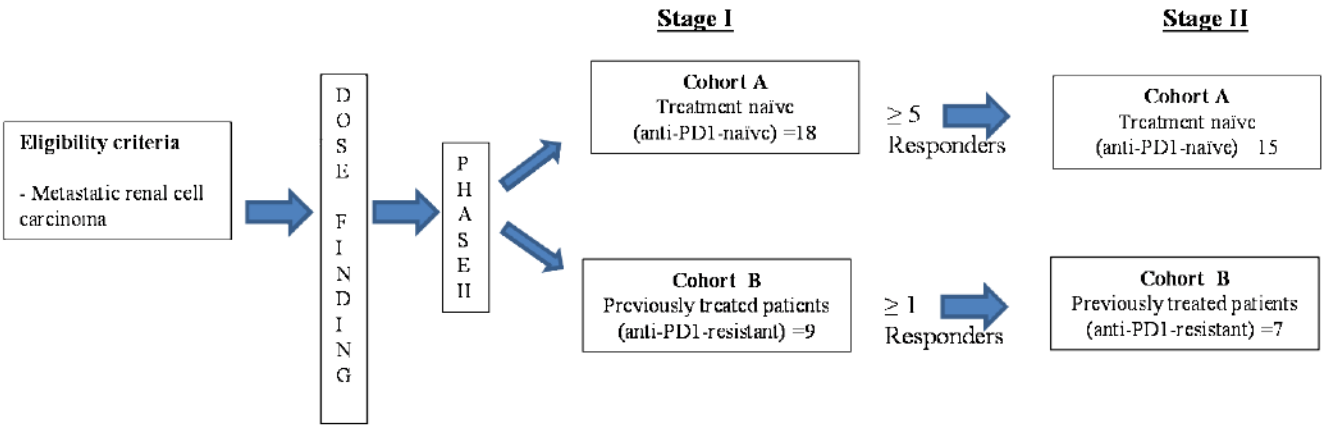
To assess the objective response rate (Phase I only), progression-free survival and overall survival

2.3 Correlative

To characterize PD-L1/2, immune cell subsets, and miRs in tumor and/or blood in correlation with response

3.0 Study Design

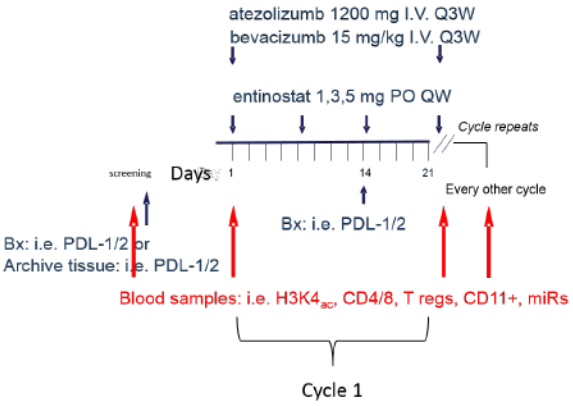
3.1 Schema



3.2 Description of the Study

This is a Phase I/II, open-label, safety, pharmacodynamics and efficacy study of atezolizumab in combination with entinostat and bevacizumab in patients with advanced renal cell carcinoma. This clinical study will be composed of a Dose Finding Phase (Phase I) and a two-stage Phase (Phase II) portion. In Phase 1 (**Schema A**: Combination Phase), patients will be treated with oral entinostat every 7 days, with bevacizumab at the fixed dose of 15 mg/kg IV every 3 weeks and with atezolizumab at the fixed dose of 1200 mg IV every 3 weeks. Each cycle length is 21 days. Three dose levels of entinostat will be tested in 3-patient cohorts according to the 3 + 3 standard design (1 mg, 3 mg and 5 mg). For the Dose Finding Phase, the starting dose level of entinostat will be 1 mg PO every 7 days. The first dose level will have a minimum of 3 patients treated (unless the first 2 patients experience DLT(s) before the 3rd patient is enrolled). DLTs attributable to entinostat and/or bevacizumab and/or atezolizumab will be evaluated during the first 21 days of the combination treatment.

Schema A: Combination Phase

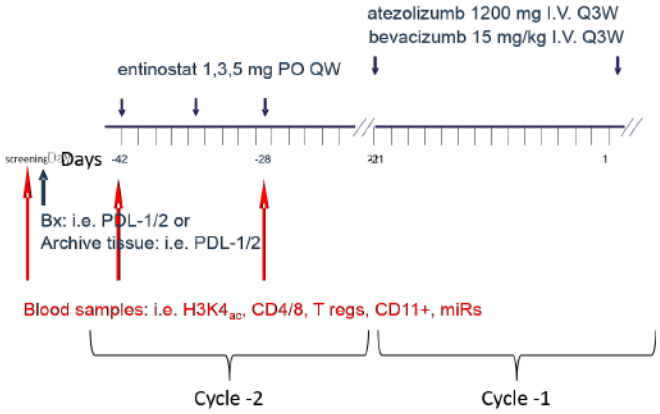


If a DLT occurs in 1 patient treated at the starting dose level, a minimum of 3 additional patients will be treated at this dose level. If DLTs occur in 2 or more of the first 6 patients, the study will be terminated. If a DLT occurs in 1 out of 6 patients, 3 additional patients will be treated at the next dose level (level 2). If no DLTs occur at the starting dose level 1, 3 additional patients will be treated at the next dose level (level 2). If no DLTs occur at the dose level 2, 3 additional patients will be treated at the next dose level (level 3). If no DLTs occur at dose level 3, this dose level will be recommended for the Phase II portion of the study. Patients who experience Grade ≥ 3

toxicity and recover to ≤ Grade 1 (or to pretreatment baseline level toxicity) may continue treatment at the next lower level. The Phase II Dose will be RP2D of entinostat (i.e., the highest tested dose that is declared safe and tolerable by the Investigators and Sponsor-Investigator).

Once the RP2D is identified, the Phase II portion (Simon's two stage design) will be opened. During Phase II, Cohorts A and B will have a Run-In period with entinostat for one cycle followed by atezolizumab and bevacizumab for the second cycle (**Schema B**), and then the Combination Phase (**Schema A**). The reason for the Run-In period is to obtain data on the immunomodulatory effects of entinostat separately from bevacizumab and atezolizumab. The run-in period will be optional for patients, including those who are rapidly progressing, or if it is in the patient's best interest clinically as determined by the treating physician's discretion. In Stage I, 27 patients with prior treatments will be enrolled in two Phase II cohorts: 18 treatment naïve (anti-PD1/PDL1 naïve) patients (Cohort A), and 9 anti-PD1 resistant (defined as patients who have been on PD1 inhibitors for at least 3 months and have progressed by either clinical or radiographic assessment) patients (Cohort B). If ≥ 5 responses are observed and confirmed in Cohort A, Stage II will be conducted with 15 additional patients. In Cohort B, if any patients has a response that is observed and confirmed, Stage II will be conducted with 7 additional patients. Patients will be treated on Cohort B with the same combination therapy as in Cohort A.

Schema B: Run-In Phase



The RP2D is the dose of entinostat, atezolizumab, and bevacizumab in combination chosen for further clinical development. Further experience in the Dose Expansion Cohort may result in a RP2D dose lower than the MTD.

Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline and every 3 cycles thereafter using RECIST version 1.1. RECIST 1.1 will be used for treatment decisions until first radiologic evidence of progressive disease (PD). Following the first evidence of radiologic PD, treatment decisions may be made by the adaption of RECIST 1.1, termed the immune-related response criteria (irRC) (see **Appendix 5**) to account for the tumor response patterns seen with atezolizumab treatment (e.g. tumor flare).

3.2.1 Definition of Dose-Limiting Toxicity (DLT)

DLTs include any Grade 3-5 toxicity related to entinostat, atezolizumab, or bevacizumab during the Dose Finding Phase (excluding ≥ Grade 3 decrease in lymphocytes, ≥ Grade 3 hypertension, ≥ Grade 3 hypophosphatemia and ≥ Grade 3 proteinuria). Grade 3 nausea or vomiting should be considered a DLT only if unresponsive to therapy and ≥ 72 hours in duration. Patients must have taken at least 2 of the 3 doses of entinostat to be considered evaluable for DLT determination. Patients who do not receive at least 75% of the expected dose of entinostat due to toxicity are considered to have DLT. Toxicity considered related to treatment that results in a delay in treatment greater than 2 weeks is also considered a

DLT. ALT > 3x ULN + Total bilirubin > 2 x ULN will be a DLT which results in permanent drug discontinuation.

Dose Level 1:

- If 0 DLTs occur in the first 3 patients enrolled to level 1, expand to dose level 2.
- If 1 DLT occurs in the first 3 patients, 3 more patients will be enrolled to expand dose level 1 to 6 patients.
- If 1 DLT occurs in 6 patients enrolled to level 1, expand to dose level 2.
- If ≥ 2 DLT occurs in the first 6 patients, the study will be terminated.

Dose Level 2:

- If 0 DLTs occur in the first 3 patients enrolled to level 2, expand to dose level 3.
- If 1 DLT occurs in the first 3 patients enrolled to dose level 2, 3 more patients will be enrolled to expand dose level 2 to 6 patients.
- If 1 DLT occurs in 6 patients enrolled to level 2, expand to dose level 3
- If ≥ 2 DLTs occur in the 3-6 patient cohort at dose level 2, the lower dose level will be considered the MTD.

Dose Level 3:

- If 0 DLTs occur at dose 3, dose level 3 is the recommended MTD. Enroll 3 additional for further evaluation of safety. If at most 1 DLT occurs in 6 patients, dose level 3 is the recommended MTD and the study will move to the Phase II portion of the study.
- If 1 DLT occurs in the first 3 patients enrolled to dose level 3, enroll 3 additional patients (total 6).
- If at most 1 DLT occurs in 6 patients, dose level 3 is the recommended MTD and the study moves to the Phase II portion of the study.
- If ≥ 2 DLTs occur in the 3-6 patient cohort at dose level 3, stop dose escalation and dose level 2 is the recommended MTD; move to the Phase II portion of the study.

Of note, under this design, a total of 6 patients will be studied at the MTD level. The objective response rate data of the 6 patients will be used for the phase II portion of the study. Depending on whether the patients have prior treatment, the objective response rate data of the 6 patients will be assigned to either cohort A or cohort B.

3.3 End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., survival follow-up) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur approximately 24 months after the last patient is enrolled.

3.4 Outcome Measures

Primary Outcome Measure
Phase I: Define a safe, tolerable Recommended Phase II Dose for the combination of atezolizumab, entinostat and bevacizumab

Phase II: Objective response rate

Secondary Outcome Measures
Objective response rate (Phase I only), progression-free survival, and overall survival

Pharmacodynamic Outcome Measures
PD-L1/2, immune cell subsets, and miRs in tumor and/or blood

4.0 Materials and Methods

4.1 Study Population

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability and willingness to comply with the requirements of the study protocol
- Age ≥ 18 years
- Measurable disease per RECIST v1.1 (see Appendix 4) for patients with solid malignancies or patients with bone disease must have disease evaluable by bone scan and/or PET scan
- Metastatic renal cell carcinoma
  - During **Phase I** - All prior treatments or none are allowed
  - During **Phase II/Cohort A** - No prior treatments with PD1 or PDL1 inhibitors are allowed
  - During **Phase II/Cohort B** - Must have at least one prior treatment with a PD1 or PDL1 inhibitor for metastatic disease for at least 3 months and have progressed by either clinical or radiographic assessment
- Life expectancy of at least 6 months
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):
  - Absolute neutrophil count (ANC) ≥ 1500 cells/μL
  - White blood cell (WBC) counts > 2500/μL
  - Lymphocyte count ≥ 300/μL
  - Platelet count ≥ 100,000/μL ; for patients with hematologic malignancies, platelet count ≥ 75,000/μL
  - Hemoglobin ≥ 9.0 g/dL
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) with the following exception:
    - Patients with known Gilbert disease who have serum bilirubin level ≤ 3×ULN may be enrolled

- Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 x ULN

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN with the following exception:
  - Patients with liver involvement: AST and/or ALT ≤ 5 × ULN

- Alkaline phosphatase (ALP) ≤ 2.0 x ULN with the following exception:
  - Patients with documented liver involvement or bone metastases: ALP ≤ 5 ×ULN

- Serum creatinine ≤ 1.25 × ULN or creatinine clearance ≥ 60 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

- Urine dipstick for proteinuria < 2+ or 24-hour urine protein < 1 g of protein is demonstrated

- International Normalized Ratio (INR) and activated Partial Thromboplastin Time (aPTT) ≤ 1.5 × ULN

  This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low-molecular-weight heparin or warfarin) should be on a stable dose.

- If a female of childbearing potential, negative serum blood pregnancy test during screening and a negative urine pregnancy test ≤ 3 days prior to receiving the first dose of study drug. If the screening serum test is done ≤ 3 days prior to receiving the first dose of study drug, a urine test is not required.
  - Non-childbearing potential is defined as (by other than medical reasons):
    - ≥ 45 years of age and has not had menses for >2 years
    - Amenorrheic for < 2 years without a hysterectomy and/or oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation
    - Post hysterectomy or oophorectomy. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound.
- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use two forms of highly effective contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of all study drugs (atezolizumab, entinostat, and bevacizumab).

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 6)

4.1.2 Exclusion Criteria

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

4.1.2.1 General Exclusion Criteria:

- Any approved anti-cancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, ≤ 3 weeks prior to first dose of study drug; however, the following are allowed:
  - Hormone-replacement therapy or oral contraceptives
  - Herbal therapy > 1 week prior to Cycle 1, Day 1 (herbal therapy intended as anti-cancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)
  - Palliative radiotherapy for bone metastases > 2 weeks prior to Cycle 1, Day 1
- Currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device ≤ 4 weeks of the first dose of study drug.
- AEs from prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia and neuropathy
- Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption.
- Bisphosphonate therapy for symptomatic hypercalcemia
- Use of bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) is allowed.
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease
- Patients with acute leukemias, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma
- Known primary central nervous system (CNS) malignancy or symptomatic CNS metastases
- Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.

  - No neurosurgical resection or brain biopsy ≤ 28 days prior to Cycle 1, Day 1
- Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No stereotactic radiation or whole-brain radiation ≤ 28 days prior to Cycle 1, Day 1
  - Screening CNS radiographic study ≥ 4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids
- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies
- Known hypersensitivity to any component of bevacizumab
- Allergy to benzamide or inactive components of entinostat
- Inability to comply with study and follow-up procedures
- Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
- Uncontrolled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg) that persists over 3 weeks and 3 consecutive measurements (each 1 week apart) despite medication.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Uncontrolled diabetes mellitus
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
  - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
  - Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of HIV infection (HIV 1/2 antibodies) or active hepatitis B (chronic or acute) or hepatitis C infection
  - Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible. HBV DNA test must be performed in these patients prior to study treatment.
  - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Clinically significant (i.e. active) cardiovascular disease (e.g., myocardial infarction or arterial thromboembolic events ≤ 6 months prior to screening or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, Grade II or greater congestive heart failure, or serious cardiac arrhythmia (see Appendix 5), or a QTc interval > 470 msec.)
- Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis ≤ 6 months of study enrollment
- Any previous venous thromboembolism > NCI CTCAE Grade 3
- History of hemoptysis (≥ ½ teaspoon of bright red blood per episode) ≤ 28 days of study enrollment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (≤ 10 days of study enrollment) use of aspirin (> 325 mg/day), clopidogrel (>75 mg/day), or therapeutic oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes
  - The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least 2 week at the time of study enrollment. Prophylactic use of anticoagulants is allowed.
- Severe infections ≤ 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection ≤ 2 weeks prior to Cycle 1, Day 1

- Received oral or IV antibiotics ≤ 2 weeks prior to Cycle 1, Day 1
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Major surgical procedure ≤ 28 days prior to Cycle 1, Day 1 or anticipation of need for a major pre-planned surgical procedure during the course of the study
- Administration of a live, attenuated vaccine ≤ 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
  - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) ≤ 4 weeks prior to Cycle 1, Day 1 or at any time during the study.
- History of abdominal fistula or gastrointestinal perforation ≤ 6 months before Cycle 1, Day 1. Serious non-healing wound, active ulcer, or untreated bone fracture (adjuvant trials: bone fractures must be healed)
- Proteinuria as demonstrated by a UPC ratio ≥ 1.0 at screening
- Malignancies other than the disease under study ≤ 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score ≤ 6, and prostate-specific antigen [PSA] ≤ 10 mg/mL, etc.)

4.1.2.2 Medication-Related Exclusion Criteria:

- Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN]- α or interleukin [IL]-2) ≤ 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with investigational agent ≤ 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) ≤ 2 weeks prior to Cycle 1, Day 1
- Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation

4.2 Study Treatment

4.2.1 Dosing Levels

Dosing Levels:	Entinostat PO Q7 days	Bevacizumab IV Q3qwks	Atezolizumab IV Q3qwks
1	1 mg	15 mg/kg	1200 mg
2	3 mg	15 mg/kg	1200 mg
3	5 mg	15 mg/kg	1200 mg

4.2.2 Study Drug: Atezolizumab

Once marketing authorization is received, commercial atezolizumab will be used and will not be provided by Genentech for “on-label” studies. For studies done before marketing authorization and/or "out of label", atezolizumab will be provided free of charge by Genentech but switched to commercial drug once marketing authorization is received. Genentech will replace any atezolizumab drug that is not reimbursed. For studies done “out of label,” atezolizumab will be provided free of charge by Genentech. The sponsor-investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Genentech requirements.

4.2.2.1 Formulation

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 a solution containing histidine acetate, sucrose, polysorbate 20 and pH 5.8.

Atezolizumab must be refrigerated at 2°C - 8°C (36°F - 46°F) 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 light.

For further details, see the atezolizumab Investigator’s Brochure.

4.2.2.2 Dosage, Administration, and Storage

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [±3] days). Atezolizumab will be administered in 250-mL 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 µm in-line filters. The IV bag may be constructed of polyvinyl chloride or polyolefin, the IV infusion line may be constructed of polyvinyl chloride or polyethylene, and the 0.2 µm in-line filter may be constructed of polyethersulfone. The use of administration supplies composed of materials other than

those listed should be avoided if possible. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. The dose solution should be stored at 2°C–25°C (36°F–77°F). The total storage time prior to administration should not exceed 8 hours. Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles≥2 at the discretion of the treating physician. 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.

For anaphylaxis precautions, see Appendix 7. Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided in Section 4.6 and Section 4.4.3, respectively.

4.2.2.3 Study Drug: Bevacizumab

Bevacizumab will be provided free of charge by Genentech. The sponsor-investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Genentech requirements.

4.2.2.4 Formulation

Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and

excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

For further details, see the bevacizumab Investigator's Brochure.

4.2.2.5 Dosage, Administration, and Storage

Bevacizumab may be supplied in 6-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI). Vials contain no preservative and are suitable for single use only.

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Keep vial in the outer carton due to light sensitivity. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C–30°C in 0.9% Sodium Chloride solution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in a controlled and validated aseptic conditions.

Bevacizumab should be prepared using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration.

The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

For further details, see the bevacizumab Investigator's Brochure.

4.2.3 Study Drug: Entinostat

Entinostat will be provided free of charge by Syndax. The sponsor-investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Syndax requirements.

4.2.3.1 Formulation

Entinostat is an oral drug supplied by Syndax as pink to light red (1 mg) or yellow (5 mg) as polymorph B coated tablets. Each tablet contains mannitol, sodium starch glycolate, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate as inert fillers. The film coating consists of hypromellose, talc, titanium dioxide, and ferric oxide pigments (red and yellow) as colorants.

For further details, see the entinostat Investigator's Brochure.

4.2.3.2 Dosage, Administration, and Storage

Entinostat is to be taken on an empty stomach, at least 2 hours after a meal and at least 1 hour before the next meal. If entinostat is vomited, dosing should not be re-administered but instead the dose should be skipped. If an entinostat dose is missed, it may be taken up to 48 hours after the scheduled dosing time. If it is not taken within the 48 hour window, the dose should not be taken and should be counted as a missed dose. The patient should take the next scheduled dose per protocol.

Entinostat is to be stored at controlled room temperature (15ºC to 25ºC) in a secure, locked storage area to which access is limited. Entinostat is to be protected from light and not to be exposed to extremes of temperature (greater than 30ºC or less than 5ºC). The pharmacist should dispense the investigational material to the patient at appropriate intervals throughout the study in childproof containers.

For further details, see the entinostat Investigator's Brochure.

4.3 Concomitant and Excluded Therapies

4.3.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and ®$_2$-adrenergic agonists; see **Appendix 7**)

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

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.1.2) should continue their use. Males and females of reproductive potential should use two methods of highly effective means of contraception.

4.3.2 Excluded Therapy

4.3.2.1 Atezolizumab

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 4.1.2 and Section 4.3.1)
  - After Cycle 1, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases); atezolizumab administration may be suspended during radiotherapy.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity
- The use of a RANKL inhibitor (denosumab) be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited for patients with solid malignancies.

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

Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

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.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of study treatment.

4.3.2.2 Entinostat

The following medications are *excluded* while the patient is receiving entinostat:

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors
- Any additional anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy, will not be allowed, even if utilized as treatment of non-cancer indications.
- Any investigational agents
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the Sponsor-Investigator. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity

The following medication *should be avoided* while the patient is receiving entinostat:

- Sensitive substrates of CYP1A2, CYP2C8, CYP3A with a narrow therapeutic window (see CYP table below)
- Drugs that are known to inhibit or induce P-gp (see P-gp table below)

Examples of substrates that may be affected by entinostat:

CYP Enzymes	Substrates with narrow therapeutic range[1]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP3A[2]	Alfentanil, astemizole[3], cisapride[3], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[3]

[1] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
[3] Withdrawn from the United States market because of safety reasons.

P-gp Inhibitors and Inducers:

Inhibitors	Inducers

Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, felodipine, lopinavir,quercetin, ranolazine,ticagrelor, ritonavir, cyclosporine, verapamil erythromycin, ketoconazole, itraconazole, quinidine	Avasimibe, carbamazepine, phenytoin, rifampin, St John's Wort, ipranavir/ritonavir

4.4 General Plan to Manage Safety Concerns

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2) and close monitoring (as indicated below and in Section 6 & 7). See Section 6.3.7 for complete details regarding safety reporting for this study.

4.4.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, and recommendations for eligibility criteria for bevacizumab and entinostat were taken into account (see Section 4.1.2).

4.4.2 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in **Appendix 1**. Patients will be followed for safety for 90 days following the last dose of study treatment or until receipt of another anti-cancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see **Appendix 1** for the list and timing of study assessments). All serious adverse events (SAEs) and protocol-defined events of special interest (see Section 6.3.4) will be reported in an expedited fashion (see Section 6.3.5). In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

4.4.3 Management of Specific Safety Concerns with 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, when clinically indicated.

Although most immune-related adverse events (irAEs) observed with Atezolizumab 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 for a given patient 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. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

4.4.3.1 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

Single agents may be held based upon toxicities, and patients who must discontinue a single agent may continue treatment with the other agents at the discretion of the investigator.

4.4.3.2 Atezolizumab

Atezolizumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.5.

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for $>$84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 6.3.6.

If a patient must be tapered off steroids used to treat AEs, atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of $\leq$ 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Sponsor-Investigator.

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology, when

clinically indicated. Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

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

Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented in this section as they have been observed in this study and are potentially immune related. See Section 4.4.4 for guidelines for the management of IRRs (see Appendix 7 for precautions for anaphylaxis).

4.4.3.2.1 Gastrointestinal Events

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in **Table 1**.

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

Table 1 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 onset [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • 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 the 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]

Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to gastrointestinal 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 does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressant 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]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab.[c] • Refer patient to gastrointestinal 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.

[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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor-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 Sponsor-Investigator.

4.4.3.2.2 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 [a] • Initiate treatment with corticosteroids equivalent 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab.[c] • 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.

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

4.4.3.2.3 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated.

Dermatologic events should be managed according to the guidelines in **Table 3**.

Table 3 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 for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after onset.[a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab.[c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[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 ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor-Investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent 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 Sponsor-Investigator.

4.4.3.2.4 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 T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g. TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Endocrine events should be managed according to the guidelines in **Table 4**.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia and altered mental status). • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.[c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 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 for life-threatening immune-related hyperthyroidism.[c]

Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to endocrinologist Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism.[c]
Symptomatic adrenal insufficiency, Grade 2-4	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c]
Hyperglycemia Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2-3	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • Initiate hormone replacement therapy if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Sponsor-Investigator. [c] • For recurrent hypophysitis, treat as a Grade 4 event.

Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Sponsor-Investigator.[c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • Initiate hormone replacement if clinically indicated.

TSH = thyroid-stimulating hormone;
MRI =magnetic resonance imaging; IV = intravenous

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 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 Sponsor-Investigator

4.4.3.2.5 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 also have 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 5.**

Table 5 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. • For Grade 1 pneumonitis, consider withholding atezolizumab
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab[c, d] • For recurrent events or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.

Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab.[c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. • 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; IVIG = intravenous immunoglobulin

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

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

4.4.3.2.6 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 6**.

Table 6 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 [a] • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better resume atezolizumab[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.[c] • For recurrent events, permanently discontinue atezolizumab.[c]

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

[a] 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Sponsor-Investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent 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 Sponsor-Investigator.

4.4.3.2.7 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Ocular events should be managed according to the guidelines in **Table 7**.

Table 7 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 [a] • 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 [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab permanently discontinue atezolizumab [c]

Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab.[c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 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 Sponsor-Investigator

4.4.3.2.8 Infusion-Related Reactions and Cytokine-Release Syndrome

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

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1, including atezolizumab. There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in **Table 8**.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ. If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Table 8 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Sponsor Investigator. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Sponsor Investigator.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or**	• Permanently discontinue atezolizumab and contact Sponsor-Investigator. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.

Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the Sponsor Investigator.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab. • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the Sponsor Investigator. • • Hospitalize patient until complete resolution of symptoms.

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

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as

oxygen delivered at > 6 L/min.

[e] 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 Sponsor-Investigator. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.
[g] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

4.4.3.2.9 Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in **Table 9,** with specific guidelines for myelitis provided in **Table 10.**

Table 9 Management Guidelines for Neurological Disorders

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

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

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

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent 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 Sponsor-Investigator.

Table 10 Management Guidelines for Immune-related Myelitis

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

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

IV = intravenous.

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

4.4.3.2.11 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, laboratory (e.g. B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. 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 12**.

4.4.3.2.12 Immune-Related Pericardial Disorders

Immune-related pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-related myocarditis. Immune-related pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability. Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac

tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11. *Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly*.

Table 12 Management Guidelines for Immune-Related Cardiac Events

Event	Management
Immune-related myocarditis, Grade 2-4 Immune-related pericardial disorders, Grades 2-4	• Permanently discontinue atezolizumab. • 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; IV = intravenous.

4.4.3.2.13 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 possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

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 corticosteroid 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]
Immune-related myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset[a]. • 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 prednisolone 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[c]. • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab.
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 limiting 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the treating investigator and the Sponsor-Investigator.

b. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent 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 agreed upon by the treating investigator and the Sponsor-Investigator.

4.4.3.2.14 Renal Events

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in **Table 14**.

Table 14 Management Guidelines for Renal Events

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

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

4.4.3.2.15 Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-related reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Clinical and laboratory features of severe CRS overlap with HLH, and HLH

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

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:

  Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)

  Platelet count < 100 × 109/L (100,000/µL)

  ANC < 1.0 × 109/L (1000/µL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:

  Platelet count ≤ 181 × 109/L (181,000/µL)

  AST ≥ 48 U/L

  Triglycerides > 1.761 mmol/L (156 mg/dL)

  Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in **Table 15** below.

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management

Suspected HLH or MAS	• Permanently discontinue atezolizumab. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Sponsor-Investigator and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015;La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH= hemophagocytic lymphohistiocytosis; IV=intravenous; MAS=macrophage activation syndrome.

4.4.3.2.16 Adverse Events of Special Interest for Atezolizumab

Adverse events of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP.

The following AEs are considered of special interest for **atezolizumab** and must be reported to the Genentech Drug Safety expeditiously (see Section 7.1.2.1 for reporting instructions), 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-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, macrophage activating syndrome, hemophagocytic lymphohistiocytosis and systemic inflammatory response syndrome
- Ocular toxicities: (e.g. uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g. atrial fibrillation, pericarditis and myocarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

These events may or may not be SAEs and they may or may not be considered related to study medication. Regardless of relationship or severity, these events will be recorded if they start from the time of the first dose of study treatment until 90 days after the last study treatment. AESIs will be followed until resolution.

4.4.3.3 Bevacizumab

Bevacizumab dose will not be reduced for reasons other than a >10% change in weight from baseline. Bevacizumab treatment may be either temporarily or permanently suspended in the case of bevacizumab-related events such as fistulae, GI perforation, hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF, wound healing complications, PRES (or RPLS) and hypersensitivity/allergic reactions in addition to any other serious bevacizumab-related toxicity (grade 3 or 4).

In addition, bevacizumab should be temporarily withheld in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since these conditions are predisposing factors for an increased bleeding tendency. To summarize, bevacizumab should be held temporarily or permanently discontinued in patients (as per the clinical judgment of the treating physician) experiencing any of the following events:

- Febrile grade 4 neutropenia and/or grade 4 thrombocytopenia regardless of the relationship to treatment (hold treatment temporarily)
- Grade ≥ 2 fistula (hold temporarily or permanently discontinue)
- GI perforation (permanently discontinue)
- Major surgery or wound healing complications (hold temporarily or permanently discontinue)
- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathy (permanently discontinue)
- Grade ≥ 3 left ventricular dysfunction (CHF) (permanently discontinue)
- Nephrotic syndrome (permanently discontinue)
- Arterial thrombosis/embolism (any grade) (permanently discontinue)
- Grade ≥ 3 venous thrombosis/embolism (hold temporarily or permanently discontinue for grade 4)
- CNS bleeding (any grade) or ≥ grade 3 bleeding of any kind (permanently discontinue)
- Grade ≥ 2 hemoptysis (hold temporarily or permanently discontinue)
- Hypersensitivity/allergic reactions related to bevacizumab (permanently discontinue)
- PRES (or RPLS) (permanently discontinue)

4.4.3.3.1 Posterior Reversible Encephalopathy Syndrome (PRES/RPLS)

There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurological disorder. PRES is also known as reversible posterior leukoencephalopathy syndrome or RPLS). PRES can

present with following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known. Adequate brain imaging using MRI must be performed as a follow-up measurement for patients with PRES.

4.4.3.3.2 Gastrointestinal Perforation and Fistula

Bevacizumab has been associated with serious cases of GI perforation in patients with mCRC and a few reports of gallbladder perforation have been reported from the post-marketing experience. The presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra-abdominal inflammation, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

Bevacizumab should be permanently discontinued in patients who develop GI perforation.

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae within the GI tract or GI tract and skin are common in patients with mCRC and ovarian cancer, but are uncommon or rare in other indications. Other fistulae (e.g. tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in post-marketing reports.

Temporarily discontinue bevacizumab in patients with grade 2 or 3 non-tracheoesophageal fistula until resolution to ≤ grade 1.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

4.4.3.3.3 Wound Healing Complications

Increased incidences of post-operative bleeding or wound healing complications have been observed in clinical trials of bevacizumab in relapsed glioma and mCRC and BC.

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed as bevacizumab may adversely impact wound healing.

In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. If the wound does not fully heal despite withholding treatment, should be permanently discontinued.

Bevacizumab therapy should be withheld for an interval of at least two half-lives (approximately six weeks) before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk-benefit assessment.

4.4.3.3.4 Hypertension

An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest the incidence of hypertension is likely to be dose-dependent.

Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy.

Blood pressure must be assessed before each bevacizumab administration.

In most cases hypertension is controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

4.4.3.3.5 Congestive Heart Failure (CHF)

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF, requiring treatment or hospitalization. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or CHF with bevacizumab.

Bevacizumab should be permanently discontinued in patients with ≥ grade 3 CHF.

4.4.3.3.6 Proteinuria

In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Proteinuria reported as an AE with bevacizumab treatment has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome with the great majority as grade 1 proteinuria. The proteinuria seen in bevacizumab clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of bevacizumab therapy. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab.

Proteinuria must be assessed by dipstick before each bevacizumab administration unless proteinuria has been determined by 24-hour urine collection. Proteinuria should be managed according to the guidelines in **Table 165** below.

Table 16 Treatment Management for Proteinuria (Bevacizumab)

NCI CTCAE v. 4.0	Urinalysis	Treatment Action
Grade 1	1+ proteinuria urinary protein < 1.0 g/24 hrs.	• No bevacizumab dose modification
Grade 2	2+ proteinuria urinary protein 1.0-3.4 g/24 hrs.	• For 2+ dipstick: may administer bevacizumab without dose modification and collect 24-hour urine prior to subsequent bevacizumab administration. • For 3+ dipstick: must obtain 24-hour urine prior to administering bevacizumab • Suspend bevacizumab for urinary protein ≥ 2 g/24 hrs. Resume bevacizumab when proteinuria is < 2 g/24 hrs.
Grade 3	urinary protein ≥3.5 g/24 hrs.	• Suspend bevacizumab. • Resume bevacizumab when proteinuria is < 2 g/24 hrs.
Nephrotic syndrome		• Permanently discontinue bevacizumab

4.4.3.3.7 Arterial thrombosis/embolism

Bevacizumab should be discontinued in patients who develop arterial thromboembolic events.

A history of arterial thromboembolic events or age greater than 65 years has been associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

4.4.3.3.8 Venous thrombosis/embolism

Bevacizumab should be held in patients developing a grade 3 thrombosis/embolism. Bevacizumab may be resumed once the patient is adequately anti-coagulated and on a stable level of anticoagulation for at least 2 weeks prior to restarting study drug treatment. Patients on heparin treatment should have an aPTT between 1.5-2.5 x ULN (or patient value before starting heparin treatment). Patients on Coumadin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1-4 days apart. Patients on full dose low molecular weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.

An increased risk of venous thromboembolic events and bleeding in patients receiving anti-coagulation therapy after first venous thromboembolic event while receiving bevacizumab has been observed.

In the event of recurrent grade 3 thrombosis/embolism, the patient should be discontinued from bevacizumab.

Bevacizumab should be discontinued in patients with life-threatening (grade 4) pulmonary embolism.

4.4.3.3.9 Hemorrhage

An increased incidence of bleeding events was observed in study patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events observed

in bevacizumab studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patient has not been prospectively evaluated in randomized clinical studies.

Bevacizumab should be permanently discontinued for:

- grade 3 or 4 bleeding of any kind
- any grade of CNS bleeding. Patients should be monitored for signs and symptoms of CNS bleeding.

Bevacizumab should be temporarily held or permanently discontinued for grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL bright red blood per episode). The safety of re-initiating bevacizumab in patients previously experiencing grade ≥ 2 hemoptysis has not been evaluated.

If hemorrhagic complications occur in patients on full dose anti-coagulation therapy, permanently discontinue bevacizumab treatment and follow guidelines of the treating institution. Standard procedures such as antagonization with protamine or vitamin K and infusion of vitamin K dependent factors should be considered dependent on the severity of the bleeding.

4.4.3.3.10 Hypersensitivity/Allergic Reactions and Infusion-Associated Reactions

Bevacizumab should be permanently discontinued in patients exhibiting hypersensitivity/allergic reactions.

The NCI CTCAE distinguish between hypersensitivity reactions and acute infusion reactions induced by cytokine release. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap.

Patients may be at risk of developing infusion reactions to bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If an infusion reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

4.4.3.3.11 Osteonecrosis of the Jaw

Osteonecrosis of the jaw was reported in patients receiving bevacizumab mainly in combination with bisphosphonates in the post-marketing setting. The pathogenesis of the osteonecrosis is unclear. For further information, please refer to the bevacizumab Investigator' Brochure.

4.4.3.3.12 Ovarian Failure

Ovarian failure has been reported more frequently in patients receiving bevacizumab. Ovarian function recovered in the majority of women after bevacizumab discontinuation. For further information, please refer to the bevacizumab Investigator' Brochure.

4.4.3.3.13 Adverse Events of Special Interest for Bevacizumab

The following AEs are considered of special interest for **bevacizumab** and must be reported to the Genentech Drug Safety expeditiously (see Section 7.1.2.1 for reporting instructions), irrespective of regulatory seriousness criteria:

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Hemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 hemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (or RPLS; any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

  These events may or may not be SAEs and they may or may not be considered related to study medication. Regardless of relationship or severity, these events will be recorded if they start from the time of the first dose of study treatment until 90 days after the last study treatment. AESIs will be followed until resolution.

4.4.3.4 Entinostat

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Sponsor-Investigator.

Dose modifications should be based on the AE requiring the greatest modification and should be properly documented in source documents. Investigators may take a more conservative approach than the guidelines outlined below on the basis of clinical judgment that is in the best interest of the subject.

Management of toxicities that are at least possibly related to entinostat, with toxicities graded by the Investigator according to the NCI, CTCAE, version 4.03 should be managed as follows:

Table 17 Management of Non-hematologic Toxicities (Entinostat)

Non-hematologic Toxicity	
Toxicity	**Dose Modifications**
Grade 4	Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline under the following directions: If recovered within 4 weeks of onset (i.e., ≤3 missed doses), resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, discontinue study treatment If not recovered within 4 weeks, permanently discontinue study drug.
Grade 3	Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline under the following directions: 1. If recovered within 1 week, resume study drug at prior dose. If not recovered within 1 week, continue to hold dose. 2. If recovered within 2-4 weeks, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, permanently discontinue study drug 3. If not recovered within 4 weeks, permanently discontinue study drug.
Recurrence of the **same** ≥ Grade 3 toxicity despite dose reduction	If the **same** ≥ Grade 3 event **recurs:** Administer symptomatic remedies/ start prophylaxis. Hold[1] dose until recovery to Grade 1 or baseline. If recovered within 2 weeks, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, permanently discontinue study drug If the **same** ≥ Grade 3 event **recurs** (i.e., third occurrence) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.
≤Grade 2	Administer symptomatic remedies / start prophylaxis. Dosing of study drug may be interrupted at the Investigator's discretion. If dose is held for 4 consecutive weeks, permanently discontinue study drug.[1] If toxicity resolves, resume entinostat at the original dose.

1 If greater than 50% of doses are missed during any 6 week period, discontinue from study drug treatment.

Table 18 Management of Hematologic Toxicities (Entinostat)

Hematologic Toxicity

Toxicity	Dose Modifications
≥Grade 3 neutropenia, ≥Grade 3 uncomplicated thrombocytopenia, or Grade 2 complicated thrombocytopenia	Administer symptomatic remedies/ start prophylaxis. Hold dose[1] until recovery to Grade 1 or study baseline under the following direction: If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose. If receiving 2 mg dose, and not recovered by either of the next 2 scheduled doses, permanently discontinue study treatment. Otherwise, skip each dose. If recovered for either of these doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg. • If receiving 3 mg, restart study drug at 2 mg. If not recovered within 4 weeks, permanently discontinue study drug.
Recurrence of the **same** hematologic toxicity	If the same hematologic toxicity recurs: 1. Administer symptomatic remedies/ start prophylaxis. Hold[1] dose until recovery to Grade 1 or baseline. 2. If recovered within 2 weeks, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, permanently discontinue study drug 3. If the same ≥ Grade 3 event recurs (i.e., third occurrence) despite entinostat dose reduction to 2 mg, as described above, permanently discontinue study drug.

[1] *If greater than 50% of doses are missed during any 6 week period, discontinue from study drug treatment.*

4.5 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor-Investigator determines it is in the best interest of the patient
- Patient non-compliance with trial treatment or procedure requirements
- Patient lost to follow-up

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate Case Report Form (CRF). However, patients will not be followed for any reason after consent has been withdrawn.

See Section 4.9.7 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

4.6 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Confirmed radiographic disease progression per irRC at time of 2nd progression
- Unacceptable adverse experiences as described in Section 4.4.4
- Intercurrent illness that prevents further administration of treatment

The primary reason for study treatment discontinuation should be documented on the appropriate CRF.

4.7 Subject Replacement Strategy

Patients who do not complete the Cycle 1 of the Dose Finding Phase will be replaced. Patients who cannot complete Cycle 1 of the Phase II for reasons unrelated to the study drug will also be replaced.

4.8 Study and Site Discontinuation

The Sponsor and/or Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor-Investigator has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

4.9 Trial Procedures

The flowchart of scheduled study assessments is provided in **Appendix 1**. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.9.1 Administrative Procedures

4.9.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature if the new information would affect the subject's willingness to continue participation in the study as determined by the IRB.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

4.9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

4.9.1.3 Registration

Each subject to sign the informed consent must be entered into the OnCore® database. Subject ID numbers are sequential by site. The site will enter the study number in OnCore when entering the consent signed date. After eligibility is confirmed, the site is responsible for completing the registration in the OnCore® database. Additional details of this process can be found in the Study Procedure Manual.

4.9.1.4 Medical History

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), prior cancer therapies and procedures. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

4.9.1.5 Prior and Concomitant Medications

All medications used by the patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies) and throughout the trial will be collected.

4.9.1.6 Trial Compliance

Subjects will be given a drug diary (see **Appendix 10**) to record doses of entinostat and any adverse events he or she may experience. Drug diaries will be collected at the start of the next cycle, or at the time of the next clinic visit, whichever is sooner. Any discrepancies in drug accountability will be clarified with the subject.

4.9.1.7 Subsequent Anti-Cancer Therapy Status

All new anti-neoplastic therapy initiated after the last dose of trial treatment will be collected. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

4.9.2 Clinical Procedures/Assessments

4.9.2.1 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

4.9.2.2 Physical Examination

A complete physical examination will be performed during the screening phase and at the treatment discontinuation visit and should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

As part of tumor assessments, a physical examination should also include the evaluation of the presence and degree of enlarged lymph nodes, skin neoplasm, hepatomegaly, and splenomegaly.

All patients should be monitored for symptoms of brain metastases. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological

examination. A CT or magnetic resonance imaging (MRI) scan of the head should be done as clinically indicated to confirm or refute new or worsening brain involvement.

4.9.2.3 Adverse Event (AE) Monitoring

Each subject will be evaluated for potential new or worsening AEs as specified in the Study Flowchart (see **Appendix 1**) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see **Appendix 3**). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

4.9.2.4 Performance Status

Eastern Cooperative Oncology Group (ECOG) status (see Appendix 6) will be assessed during the screening phase, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Study Flowchart (see **Appendix 1**).

4.9.3 Tumor and Response Assessment

Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. RECIST 1.1 will be used for treatment decisions until first radiologic evidence of progressive disease (PD). Following the first evidence of radiologic PD, treatment decisions may be made by the adaption of RECIST v1.1 (see **Appendix 4**), termed the immune-related response criteria (irRC) (see **Appendix 5**) to account for the tumor response patterns seen with atezolizumab treatment (e.g. tumor flare). CT modalities should be done according to standard of care for the patient's disease. Bone scans should be done at baseline and then only as clinically indicated.

4.9.4 Laboratory Assessments

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory per institutional standard operating procedures.

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, and Amylase/Lipase)
- Coagulation (aPTT and INR)
- Pregnancy test (for women of childbearing potential, including women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein (creatinine [UPC] ratio or dipstick), ketones, and blood)
- HgbA1c labs are only required for patients with pre-existing condition of diabetes mellitus. Thyroid function testing (TSH, free T3, and free T4), Epstein-Barr virus (EBV) serology (EBNA IgG), hepatitis B virus (HBV) serology (HBsAg, antibodies

against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated

- HBV DNA test is required for patients who have known positive serology for anti-HBc
- HCV RNA test is required for patients who have known positive serology for anti-HCV

4.9.5 Treatment Compliance for Entinostat

Treatment compliance to entinostat will be assessed at the end of each cycle. Patients will complete a diary to document their weekly intakes. They will be instructed to return all unused drugs (partially used and empty containers) and their diary at the end of each cycle. Site staff will perform accountability of the returned drug and will assess patient compliance. Site staff must ensure that the patient clearly understands the directions for self-medication and follows the schedule. The trial drug diary can be found in Appendix 10.

4.9.6 Correlative Studies

Correlative blood and fresh tissue studies will be analyzed at the coordinating center. Please refer to the Study Procedures Manual for specific details. The following assessments will be performed:

4.9.6.1 Blood Samples

Blood samples should be collected prior to treatment administration whenever possible.

Biomarker assays will be done to examine:

- CD45 cells
- Effector CD4 T cells
- Effector CD8 T cells
- FoxP3+ CD4+ Regulatory T cells (Tregs)
- CD11b+ CD14+ HLA-DR low/neg MDSCs
- Circulating microRNAs

4.9.6.2 Tissue Samples

Archival Tissue

PD-L1 expression by immunohistochemistry will be performed by a Genentech designated lab. An IHC-based scoring criteria has been formulated to represent PD-L1 expression on tumor cells (TCs) and on immune cells (ICs). The definition of PD-L1 positivity varies by tumor type and is being investigated in ongoing trials in the atezolizumab clinical development program. Please refer to the atezolizumab Investigator's Brochure for further details regarding the IHC scoring algorithm.

Whenever possible, archival tissue samples will be obtained from any time prior to drug dosing from either the original diagnosis or from any subsequent biopsy (including from

a metastatic lesion) done prior to start of first drug treatment. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 4 unstained slides, with an associated pathology report, for central testing of tumor PD-L1 expression by a Genentech designated lab. Patients who do not have archival tissue specimens available may undergo an optional biopsy during the screening period (applies to run-in and combination phases) and during Cycle 1 on Day 14 of the combination phase under the following conditions:

1) Agreement indicated per documentation on the informed consent, and

2) Disease which is suitable for PD-L1 expression testing per the requirements listed below.

- Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

- Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
- Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

Missed biopsies for patients who meet all of the above requirements will not be considered protocol deviations for the purposes of this study.

Fresh Tissue

Biomarker assays will be done to examine:

- PDL-1/2
- T effector cells
- Tregs
- MDSCs
- M1/M2 macrophages

Pretreatment and On Treatment tumor biopsy samples will be collected from patients who consent and who have accessible tumor per institutional procedures. The biopsy sample will be split into **two** portions: one (1) portion will be placed in RNA*later*™ and one (1) portion will be placed in 10% formalin solution.

The On Treatment samples will be collected ~2 hours following the most recent dose of entinostat on cycle 1 day 14. To ensure that these samples are obtained at the correct time, patients are urged to take their entinostat dose in the clinic on the day of on-treatment sample collection. The time of the entinostat dose and sample collection must be recorded.

4.9.7 Treatment Discontinuation Visit

Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit.

4.9.8 Safety Follow-Up

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

4.9.9 Follow-Up

Subjects who discontinue trial treatment for a reason other than disease progression will move into the follow-up phase and should be assessed per institutional guidelines by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

4.9.10 Survival Follow-Up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted every 6 months (± 30 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.9.11 Retreatment Phase

Subjects who stop atezolizumab with stable disease or better may be eligible for up to one year of additional atezolizumab therapy if they progress after stopping study treatment. This retreatment phase is only available if the study remains open and the subject meets the following conditions:

EITHER

- Stopped initial treatment with atezolizumab after attaining an investigator-determined confirmed complete response according to RECIST 1.1 (Section 14.3), and
    - Was treated for at least 24 weeks with atezolizumab before discontinuing therapy
    - Received at least two treatments with atezolizumab beyond the date when the initial complete response was declared

OR

- Had stable disease, partial response, or complete response and stopped atezolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with atezolizumab
- Did not receive any anti-cancer treatment since the last dose of atezolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 6 months after the last dose of study medication (reference Section 5.5.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 6 months after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects will have the opportunity to continue to be treated beyond the first sign of disease progression per RECIST 1.1 if the treating physician believes that the subject is receiving clinical benefit from the treatment. Subjects will be allowed to receive concomitant surgical therapy with the approval of the Sponsor-Investigator if they feel the subject would receive clinical benefit from the treatment.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received atezolizumab. Treatment will be administered for up to one additional year. Subjects should be re-consented prior to start of re-treatment.

Visit requirements are outlined in **Appendix 1** Study Flowchart.

5.0 Statistical Considerations

5.1 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical

variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below. All analyses will be separate for Phase I and Phase II. Within Phase I, analysis will be separate for each dose level. In Phase II, analyses will be separate for each cohort.

5.2 Study Design

This is an open-label Phase I/II clinical trial. No randomization or blinding is involved. There are two cohorts in Phase II, Cohort A is anti-PD-1 naïve and Cohort B is anti-PD-1 resistant.

5.3 Analysis Populations

5.3.1 Efficacy Population

The efficacy population comprises all patients who meet the eligibility criteria, are registered onto the study, get at least one dose of study drug, and have at least one follow-up evaluation. This set will be used for efficacy analysis.

5.3.2 Safety Population

The safety population comprises all patients who have received at least one dose of the study medication. This set will be used for safety analysis.

5.4 Sample Size, Accrual and Study Duration

A minimum of 3 (if lowest dose in Phase I is not safe and tolerable) and maximum of 61 subjects will be enrolled in this study. The sample size justifications will be described in the next few paragraphs. We will enroll up to 72 patients to allow for about 10% rate for patients not evaluable for either toxicity or efficacy. Accrual is estimated to about 1.2 patients per month. The accrual duration is expected to take up to 60 months.

The maximum sample size for Phase I is 18 (maximum 6 for each dose level by the 3+3 design described earlier). Subjects not evaluable for toxicity in the dose finding stage of the trial will be replaced. A total of 6 evaluable patients will be studied at the MTD level, whose response data will be used towards to the phase II portion of the study. This is important: the data of the 6 evaluable patients will be assigned to either Cohort A or Cohort B, depending on whether they have prior treatment.

The maximum statistical sample size requirement is 49 (33+16) for the Phase II of the study. Since the response rate data from the 6 evaluable patients at the MTD level will be used, we only need to accrue 43 additional evaluation patients. The maximum sample size requirement is thus 61 (18+43).

The study design and sample size for the Phase II portion is justified as follows. Cohort A (anti-PD-1 naïve) will use the Simon's Minimax two-stage design. The Minimax two-stage design will test a one-sided hypothesis that the null response rate is 20% versus the alternative rate of 40%. A total sample size of 33 evaluable patients will be accrued over two stages. In the first stage, 18 patients will be accrued. If among the 18 patients, 4 or fewer patients have tumor response, then the accrual to this cohort will be stopped. Otherwise, 15 additional patients will be accrued for a total of 33. The trial is considered a success when the null hypothesis is rejected, which will happen when if 11 or more patients

have tumor responses among the 33 patients. The trial has an expected sample size of 22.25 and a probability of early termination of 0.716. If true response rate is 20%, there is a 0.046 probability of concluding that it is (type-I error). If true response rate is 40%, then the power of the study is 80%.

Cohort B (anti-PD-1 resistant) will also a Simon's optimal two-stage design. The null hypothesis that the true response rate is 2.5% will be tested in one-sided against an alternative rate of 20%. A total sample size of 16 evaluable patients will be accrued over two stages. In the first stage, 9 patients will be accrued. If among the 9 patients, no patient has tumor response, then the accrual for this cohort will be stopped. Otherwise, 7 additional patients will be accrued for a total of 16. The null hypothesis will be rejected if 2 or more patients have tumor responses among the 16 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 20%. The expected sample size is 10.43 and the probability of early stopping is 0.80 when the true response is only 2.5%.

Of note, an evaluable patient is defined as a patient who has taken at least one cycle of treatments and with at least one subsequent tumor response data who can finish the study treatment and have the response data measured. Assuming a 10% drop-out rate, then Cohort A is anticipated to accrual a total 37 patients, and Cohort B is anticipated to accrual a total 18 patients.

5.5 Significant Protocol Violations

Significant protocol violations such as with respect to eligibility criteria and treatment plan will be tabulated.

5.6 Patient Characteristics

Baseline patient characteristics will be tabulated, such as demographics (age, race, gender) and disease characteristics.

5.7 Concomitant Medications

Drugs that might affect the study medication will be tabulated.

5.8 Exposure and Compliance

Exposure to the study medication will be summarized by frequencies and rates of the doses given. Reasons of not completing all doses will be tabulated.

5.9 Efficacy and Correlative Analysis

For each Phase and Cohort, responses will be tabulated and objective response (CR+PR) via RECIST 1.1 will be summarized with the point estimate and corresponding exact 95% confidence interval. Progression free and overall survival will be estimated using standard Kaplan-Meier curves. The median time-to-event for each endpoint will be estimated along with the corresponding 95% confidence interval. Similar descriptive analyses will be performed using irRC criteria. Correlative endpoints such as quantitative characteristics of humoral immune response will be characterized by their mean and corresponding 95% confidence interval. For Phase II, Cohort A, baseline and/or changes in correlative endpoints will be correlated with response by logistic or Cox regression. No statistical comparisons are planned between cohorts. Analyses will be done separately by each cohort in Phase II. Patients enrolled in the Dose Finding Phase will not be included in Phase II.

5.10 Safety Analysis

Toxicities according to CTCAE 4.0 (see Section 14.2) will be summarized by frequencies and rates calculated as the proportion of patients in the safety population experiencing SAEs, discontinuations due to AEs, and AEs. Two sets of tables will be generated: one for the overall toxicities and one for toxicities related to the study medication (possibly related, probably related and definitely related). Toxicities will be grouped by system using MedRA preferred terminology. Grade 1 to 4 will be reported individually and also as Grade 3/4. Deaths will be reported individually. AEs will be reported by dose finding cohort. In the Dose Finding Phase, DLT's will be evaluated in the first 21 days of therapy (see Section 5.2.1.3). The AEs during Phase II will also be reported separately by cohort (anti PD1-naïve vs resistant).

Toxicity monitoring in the Phase II cohorts will be done for each cohort separately. In each cohort, toxicity monitoring will be evaluated for about 6 patients as listed in the table below. The stopping rule in the table blow is based on the method of repeated significance testing. We will consider the treatment to be excessively toxic if the probability of DLTs in the first 21 days of therapy is 33% or greater. The toxicity is acceptable if the probability is 15% or less. The toxicity stopping rule will be based on the following table:

Stop if number of patients with DLT is greater than or equal to:	3	5	5	6	8	9
Among the cumulative number of patients	6	12	14	18	24	30

Pneumonitis Stopping Rules

Per Genentech, the incidence of pneumonitis in subjects with Renal Cell Carcinoma receiving Atezolizumab + Bevacizumab was reported as 3% (for all grades) and <1% (for grades 3-4) in a study with 451 total subjects treated. During the phase II portion of the trial, we will use a toxicity monitoring rule based on the repeated significance testing to ensure the incidence of patients with grade 3-4 pneumonitis is not excessive. Assuming that ≤3% grade 3-4 pneumonitis are acceptable, but ≥5% is excessive, the enrollment will be put on hold when the following numbers of patients with grade 3-4 pneumonitis are observed among varying cohort sizes. When the enrollment halt happens, the DSMC will be informed and consulted.

Hold if number of patients with grade 3-4 pneumonitis is greater than or equal to:	2	3	4	5
Among this cumulative number of patients	1-7	8-19	20-34	35-40

5.11 Interim Analysis

A formal interim efficacy analysis will be performed for Cohort A and Cohort B of Phase II as described above. No other formal interim efficacy analysis is planned. Safety stopping rule will be implemented as described below.

6.0 Assessment of Safety

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to atezolizumab, all events of death, and any study-specific issue of concern.

6.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related AEs, specifically the induction or enhancement of autoimmune conditions. AEs with potentially immune-related causes, including IRR, immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barre syndrome, myasthenia syndrome/myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders,, nephritis, myositis, and severe cutaneous adverse reactions.

In addition, immune–mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Section 4.4.3 Management of Specific Safety Concerns with Atezolizumab of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A more detailed safety profile of atezolizumab is provided in the atezolizumab Investigator's Brochure.

6.2 Risks Associated with Bevacizumab

Clinical experience with bevacizumab has shown significant AEs associated with its use. Patients particularly vulnerable to significant AEs, such as those with recent pulmonary hemorrhage/hemoptysis or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding, have been excluded from the study. Study patients will be assessed by prior medical history, physical examinations, monitoring of vital signs, performance status evaluations, hematology and chemistry laboratory testing, urinalyses and ECGs.

Concomitant medication use, AEs and SAEs will also be closely monitored throughout the study. All AEs will be graded according the NCI CTCAE v. 4.0.

Refer to the Avastin® (bevacizumab) Investigator's Brochure for a more details.

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard

public health guidelines is recommended for patients on treatment with or without bevacizumab.

- Proteinuria will be monitored by urine protein: creatinine (UPC) ratio or dipstick at least every 6 weeks.

- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

6.3 Safety Parameters and Definitions

6.3.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

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 renal cell carcinoma 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
- Pre-existing 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

6.3.2 Attribution

Attribution is the determination of whether an adverse event is related to the study drug or a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug/procedure/treatment.

Probable: The adverse event is likely related to the study drug/procedure/treatment.

Possible: The adverse event may be related to the study drug/procedure/treatment.

Unlikely: The adverse event is doubtfully related to the study drug/procedure/treatment.

Unrelated: The adverse event is clearly NOT related to the study drug/procedure/treatment.

6.3.3 Unanticipated Problem (UP)

Any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being study;

2. related or possibly related to participation in the research; and

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs

6.3.4 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

6.3.5 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate Institutional Review Boards (IRBs), Syndax, and Genentech, Inc., in accordance with CFR 312.32 (Investigational New Drug [IND] Safety Reports).

6.3.6 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 90 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

6.3.7 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, bevacizumab or entinostat (see following guidance), and actions taken.

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

Yes(definitive, probable, possible, unlikely)

- There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab, bevacizumab or entinostat, 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 atezolizumab, bevacizumab or entinostat ; and/or the AE abates or resolves upon discontinuation of atezolizumab, bevacizumab or entinostat or dose reduction and, if applicable, reappears upon re-challenge.

No (unrelated)

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

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

6.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

6.4.1 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?"

6.4.2 Specific Instructions for Reporting Adverse Events

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

6.4.2.1 Diagnosis versus 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.

6.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 6.3.6), 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." Deaths that occur during the protocol-specified adverse event reporting period (see Section 6.3.6) that are attributed by the investigator solely to progression of disease should be recorded only in the study CRF.

6.4.2.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

6.4.2.4 Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing 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.

6.4.2.5 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE version 4.0 (See APPENDIX 3) 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 (v4.0), 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

6.4.2.6 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of study drug. A report should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via fax to Genentech and Syndax Drug Safety. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. 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 subject exposed to atezolizumab, bevacizumab or entinostat should be reported as an SAE.

6.4.2.7 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. Male patients who received study treatment should not attempt to father a child until end of study. A report should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and faxed to Genentech and Syndax Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. Once the authorization has been signed, the investigator will update the Pregnancy Report CRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Sections C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

• Protocol number and title description

• Description of event, severity, treatment, and outcome if known

• Supportive laboratory results and diagnostics (Section B.6)

• 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., initials, 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

https://www.fda.gov/media/69876/download

6.4.2.8 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 atezolizumab and/or bevacizumab exposure. 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 adequately the coordinating center who will then adequately report to Genentech drug safety during follow-up period.

6.4.2.9 Safety Reconciliation/ Case Transmission Verification of Single Case Reports

The sponsor-investigator 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 and Syndax in the preceding time period.

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

If discrepancies are identified, the Sponsor-Investigator, Genentech and Syndax 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-investigator 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.

6.4.2.10 Adverse Events of Special Interest

Adverse events of special interest (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-Investigator 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-Investigator to other parties (e.g., Regulatory Authorities) may also be warranted.

Non Drug Specific Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
- Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Data related to a Suspected transmission of an infectious agent by the study treatment (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 study treatment is suspected

The AEs listed in Section 4.4.3.2.14 are considered of special interest for **atezolizumab** and must be reported to the Genentech Drug Safety expeditiously (see Section 7.1.2.1 for reporting instructions), irrespective of regulatory seriousness criteria.

The AEs listed in Section 4.4.3.3.13 are considered of special interest for **bevacizumab** and must be reported to the Genentech Drug Safety expeditiously (see Section 7.1.2.1 for reporting instructions), irrespective of regulatory seriousness criteria:

These events may or may not be SAEs and they may or may not be considered related to study medication. Regardless of relationship or severity, these events will be recorded if they start from the time of the first dose of study treatment until 90 days after the last study treatment. AESIs will be followed until resolution.

7.0 Adverse Event Reporting

7.1 Participating Site Reporting Responsibilities

7.1.1 Reporting SAE's and Pregnancy to the Coordinating Center (IU Simon Comprehensive Cancer Center)

Any serious adverse event, unanticipated problem, event of clinical interest occurring from the first dose of investigational product to within 90 days from the last dose of investigational product must be reported to the IU Simon Comprehensive Cancer Center within **1 business day** of notification or discovery of the incident, using the IUSCCC SAE form. Any reports of pregnancy from the first dose of investigational product to within 6 months or pregnancy from the last dose of investigational product must also be reported to the IU Simon Comprehensive Cancer Center within **1 business day** of notification or discovery. This form must be accompanied by a cover letter which: identifies the event, is signed by the local principal investigator or treating physician, includes the applicable study number and title, and contains the following (refer to SPM for cover letter):

- Site assessment of the event attribution to investigational treatment or study procedure

- Site assessment of event expectedness (expected vs. unexpected)

- Assessment of whether or not the research places subjects at a greater risk of harm than was previously known or recognized

- Assessment of the event's effect on the risk to benefit ratio

- Statement as to whether the informed consent statement should reflect changes in the potential risks involved

- Statement as to whether the event has been reported previously, and if so, whether the frequency is considered unusually high

Send to: IUSCC Clinical Trials Office
ATTN: Multicenter coordinator/ IUSCC-0574
E-mail: IUSCCSAE@iu.edu
Backup Fax: (317) 944-3601

All SAEs must also be entered into OnCore for **monthly review** by the DSMC Coordinator. The Multicenter Network Associate Administrator, or designee, will distribute all reports meeting expedited reporting criteria to all participating sites, the FDA, Genentech and Syndax. Copies of all serious adverse event reports will be kept on file in the IU Simon Comprehensive Cancer Center Clinical Trials Office.

7.1.2 Reporting to the IRB

Each participating site will report SAEs, pregnancies, and unanticipated problems to their IRB per local and institutional guidelines.

7.1.2.1 Coordinating Center Reporting Responsibilities

The sponsor-investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Product Complaints (with or without an AE) and Special Situation Reports (including pregnancy reports) originating from the Study for the Product.

Sponsor-Investigators must report all Adverse Events/Serious Adverse events (SAEs), AEs of Special Interest (AESIs), Product Complaints (with or without an AE) and Special Situation Reports (including pregnancy reports) must be reported to Genentech and Syndax within the timelines described below using the IUSCCC SAE form. The completed SAE/case report should be sent immediately upon completion to:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

- Genentech Drug Safety at Email usds_aereporting-d@gene.com or Fax **(650) 238-6067**
- Syndax at Email SyndaxSAEReporting@syndax.com or Fax **(781) 419-1420**

All Product Complaints without an AE should be reported to:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date of the adverse event or laboratory values received after the report) must be documented on a follow-up report as soon as that information becomes available and/or upon request. A final report to document resolution of the SAE is required. See Section 7.1.2.2 and 7.1.2.3below for more details regarding initial, follow-up and final reports.

SAE reports and AEs of Special Interest (Genentech only, Section 6.4.2.10), whether related or unrelated to the investigational product(s), will be transmitted to Genentech and Syndax within one (1) business day (unless otherwise noted) of the Awareness Date.

Note: Investigators should also report events to their IRB as required.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), Product Complaints (with or without an AE) and other Special Situation Reports where the patient has been exposed to the Genentech Product, will be sent on a IUSCCC SAE Formto 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.

- **AESIs**

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

- **Special Situation Reports**

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

  - **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 6 months 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.

- **Other Special Situation Reports**
  In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the Product usage during breastfeeding
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

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

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

  The sponsor-investigator will be responsible for collecting all product complaints and submitting them to the appropriate pharmaceutical company.

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

7.1.2.2 SAE Reporting Form Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within IUSCCC SAE 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 AE to each investigational product and suspect medication

7.1.2.3 Follow-Up Information

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

- Adding to the original IUSCCC SAE Reporting Form and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original IUSCCC SAE Reporting Form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE 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.)

Occasionally Genentech or Syndax may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety or Syndax representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety and Syndax as soon as it becomes available and/or upon request.

7.1.3 Additional Reporting Requirements for IND

For investigator-sponsored IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

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

The IUSCC Protocol Development Coordinator should be contacted to assist with all FDA submissions and will be provided with a copy of all events that are reported to the FDA.

All IND submissions will be maintained in a master file in the IUSCC Clinical Trials Office.

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

7.1.3.1 7 Calendar Day Telephone or Fax Report

The investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of the investigational product(s). An unexpected AE is one that is not already described in the Investigator's Brochures. Such reports are to be telephoned or faxed to the FDA, Syndax and Genentech within 7 calendar days of first learning of the event.

7.1.3.2 15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of the investigational product(s). An unexpected AE is one that is not already described in the Investigator's Brochures.

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, Syndax 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).

Contact Information for IND Safety Reports
FDA fax number for IND safety reports:

Fax: (800) FDA-0178

All written IND safety reports submitted to the FDA by the investigator must also be faxed to the following:

Genentech Drug Safety Fax: (650) 225-4682 or (650) 225-4630

Email: ctvistsa@gene.com

Syndax: SyndaxSAEReporting@syndax.com (email) or (781) 419-1420 (fax)

Site's IRB: IU Office of Human Subjects via the IUSCC CTO

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

Tel: (888) 835-2555

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

7.1.3.3 IND Annual Reports

Copies of all IND annual reports submitted to the FDA by the Sponsor-investigator should be sent to:

Genentech Drug Safety CTV mailbox: Email: ctvistsa@gene.com

Syndax: SyndaxSAEReporting@syndax.com (email) or (781) 419-1420 (fax)

7.2 Study Close-Out

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

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

Email: anti-pdl-1-mpd3280a-qsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvistsa@gene.com

7.3 Queries

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

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

7.4 SIGNAL MANAGEMENT AND RISK MANAGEMENT

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that Sponsor-investigator, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Sponsor-investigator issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Sponsor-investigator with signal and risk management activities related to the Product within the Study.

Genentech will also provide Sponsor-investigator with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

7.4 Reporting to Participating Sites

For IND safety reports originating from this study, IUSCC will distribute reports which are serious, unexpected and suspected to be associated with the study intervention (possibly, probably or definitely related) to all participating sites in the form of an Expedited Safety Report (external safety/IND report) within 15 calendar days from determination that the suspected adverse reaction qualifies for reporting. Copies of these Expedited Safety Reports will be kept on file in the IU Simon Comprehensive Cancer Center Clinical Trials Office.

When the sponsor(s) sends IND safety reports from external studies that involve the study drug to the Multicenter Network Associate Administrator, or designee. The Multicenter Network Associate Administrator, or designee, will forward the safety reports to the sponsor-investigator, or designee, who will review these reports and determine if revisions are needed to the protocol or consent. IUSCC will forward these reports to participating sites every 2 weeks. If an adverse event or SAE requires modification of the informed consent, protocol, or other study documents, participating sites will be informed by way of an amendment and during teleconferences, or sooner, as deemed necessary by the Principal Investigator.

8.0 Data Safety Monitoring

8.1 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) of the Indiana University Simon Comprehensive Cancer Center (IUSCC) is responsible for patient safety and privacy protection, compliance with required reporting, and study integrity for all trials conducted at IUSCC. Members are subject matter experts from multiple disciplines including medical oncology, pediatrics, biostatistics, behavioral oncology, radiation oncology, urology, surgery, gynecologic oncology, data and project management and research administration who are appointed by the DSMC Chair. The DSMC will provide independent oversight of the clinical trial so that study integrity is assured. However, the DSMC is not serving as a Data and Safety Monitoring Board (DSMB) for this study. The DSMC will meet per the currently approved DSMP, led by the DSMC Chair and Coordinator, and will review all adverse events, monitoring and auditing reports, unanticipated problems and study non-compliance events that require expedited reporting. Meeting minutes will be maintained in the IUSCC Clinical Trials Office (CTO). Specifically the DSMC has the following responsibilities:

- Assessment of the adequacy of trial-specific Data Monitoring and Safety Plan (DSMP) of studies that are not subject to external monitoring, including investigator initiated studies, and establish risk based monitoring determination of trial specific DSMB.

- Review safety data for investigator initiated trials including all adverse events, unanticipated problems and study non-compliance events requiring expedited reporting.

- Conduct routine study monitoring and auditing in compliance with the IUSCC data quality control review process.

8.2 Data Safety Monitoring Plan

This trial will comply with the current requirements of the Data and Safety Monitoring Plan (DSMP) of the IUSCC. The CTO of the IUSCC will be the Coordinating Center for this multicenter phase I trial.

In accordance with the DSMP of the IUSCC, investigators will conduct continuous review of data and patient safety. **Weekly** review meetings during Phase I are required and will include the: principal investigator, clinical research specialist, and/or research nurse data manager and/or study coordinator, and other members as per the principal investigator's discretion. In addition, **conference calls** with investigators and staff at participating sites will be scheduled **at least weekly** during Phase I while patients are on treatment (and more often as needed) to discuss study progress. If there are no patients on treatment or in follow-up, email communication will be used in lieu of a teleconference. Meeting summaries will include and document review of data and patient safety by including for each dose level: the number of patients, significant toxicities as described in the protocol, dose adjustments, responses observed, eligibility of patients enrolled at each site, serious adverse events (SAEs) or unanticipated problems (UPs) (both IUSCC and those reported from other institutions), dose adjustments, DLTs and protocol deviations. Meeting minutes will be submitted and reviewed by the DSMC at dsmc@iupui.edu.

- **Study Auditing and Monitoring:** All trials are subject to auditing and/or monitoring per the currently approved DSMC Charter.

- **Reporting Guidelines:** The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed the direct view of reports within the Clinical Trial Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

- **Reporting Death:** Death will be captured in the Case Report Form and reported per local IRB reporting guidelines.

- **Study Accrual Oversight:** Accrual data will be entered into the IU Simon Comprehensive Cancer Center OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

- **Continuing Review:** All Continuing Reviews (CR) will be reviewed annually or as dictated by the Institutional Review Board. Participating sites will submit a copy of the CR with attachments to the IUSCC Multicenter Clinical Research Coordinator.

- **Protocol Deviations:** Investigators are required to submit protocol deviations to the DSMC via the OnCore® database.

- **Early Study Closure:** At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the DSMC. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

9.0 Multicenter Guidelines

9.1 Study Documents

Each participating site must submit regulatory documents (informed consents, 1572s, Financial Disclosures, IRB approval documents, Continuing Reviews, Amendments, patient brochures or recruitment material etc.) to the Coordinating Center. The Coordinating Center will provide each site with a comprehensive list of the required documents prior to study start-up, throughout the duration of the study and upon study closeout. It is the responsibility of the participating site to maintain copies of all documentation sent to the Coordinating Center.

9.2 Study Initiation

Before activating the clinical trial at each participating site, the IUSCC CTO Multicenter Network Associate Administrator, or designee, will ensure that:

- Full Institutional Review Board (IRB) approval has been obtained.

- Research staff at the participating site has been trained in data entry into OnCore®

- A start-up meeting with each institution has taken place via telephone conference. The start-up meeting will cover protocol details (including eligibility criteria, treatment plan, etc.), responsibilities of the participating investigators, and reporting procedures.

- A financial conflict of interest statement from each investigator has been obtained.

9.3 Patient Enrollment

After eligibility is confirmed by the participating site staff, a completed eligibility checklist, supporting source documentation, and signed consent will be sent to IUSCC for verification. The Multicenter Network Associate Administrator, or designee, will return the enrollment information to the site. The site staff will then register the patient in OnCore®.

9.4 Data Monitoring

All multicenter investigator initiated trials conducted at the IUSCC are subject to data monitoring by the Multicenter Network Associate Administrator, or designee. External sites will be notified of upcoming monitoring visits and will be expected to provide the Multicenter Network Associate Administrator, or designee, with source documents for remote

monitoring of patients. Queries will be issued in OnCore® and a detailed monitoring report will be provided to the participating site. The IUSCC will also forward any monitoring and/or auditing reports to the DSMC.

When a patient enrolled on this trial, or the trial itself, is selected for local monitoring or auditing, the participating site will forward the results to the Multicenter Network Associate Administrator, or designee. In addition, if a participating site patient is selected for local auditing by the IUSCC DSMC, the site will be responsible for sending IUSCC de-identified source documents.

9.5 Record Retention

All documentation of adverse events, records of study drug receipt, dispensation, destruction, and all IRB correspondence will be stored in accordance with all applicable federal guidelines. Following closure of the study, each participating site will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

9.6 Data Acquisition

Case Report Forms and Data Submission: This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore® at https://cancer.iu.edu/oncore. The OnCore® database is a comprehensive database used by the IUSCC CTO and supported by the Indiana University Cancer Center.

Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data. All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Comprehensive Cancer Center per the DSMC Charter.

10.0 Ethical Considerations

10.1 Compliance with Laws and Regulations

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive atezolizumab treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.5.

10.2 Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the

subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

10.3 Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech or Syndax (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

10.4 Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech and Syndax representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

11.0 Study Sponsor-Investigator Requirements

This clinical research study will be monitored both internally by the Study Sponsor-Investigator and externally by the Indiana University IRB. In terms of internal review, the Sponsor-Investigator will continuously monitor and tabulate AEs. Appropriate reporting to the Indiana University IRB will be made. The Sponsor-Investigator of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,

- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

11.1 Study Medication Accountability

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

11.2 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the Indiana University IRB.

11.3 Retention of Records

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

12.0 References

1. Ferlay, Jacques, et al. "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012." *International journal of cancer* 136.5 (2015): E359-E386.

2. Fisher, Rosalie, Martin Gore, and James Larkin. "Current and future systemic treatments for renal cell carcinoma." *Seminars in cancer biology*. Vol. 23. No. 1. Academic Press, 2013.

3. Motzer, Robert J., et al. "Nivolumab versus everolimus in advanced renal-cell carcinoma." *New England Journal of Medicine* 373.19 (2015): 1803-1813.

4. Kato, Yukihiko, et al. "Synergistic in vivo antitumor effect of the histone deacetylase inhibitor MS-275 in combination with interleukin 2 in a murine model of renal cell carcinoma." *Clinical Cancer Research* 13.15 (2007): 4538-4546.

5. Shen, Li, et al. "Class I histone deacetylase inhibitor entinostat suppresses regulatory T cells and enhances immunotherapies in renal and prostate cancer models." *PLoS One* 7.1 (2012): e30815.

6. Bellmunt J, Petrylak DP, Powles T, et al. Inhibition of PD-L1 by atezolizumab leads to clinical activity in pts with metastatic urothelial bladder cancer (UBC). Ann Oncol 2014;25(Suppl 4):iv280□iv304.

7. Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti□CTLA-4 antibodies across clinical indications. Semin Oncol 2010;37: 499□507.

Appendix 1 Study Calendar

Trial Period:	**Screening Phase**		**Run-In Phase[21]**		**Combination Phase**									**End of Treatment**	**Post-Treatment**		
										To be repeated beyond 8 cycles				Discontinuation	Safety Follow-up[1]	Follow-up Visits[2]	Survival Follow-up
Treatment Cycle	Screening		C-2	C-1	C1	C1 D14	C2	C3	C4	C5	C6	C7	C8				
Scheduling Window (Days):	Within 28 days of start of tx	Within 14 days of start of tx	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	30 days post discon ± 3	Per institutional guidelines	Every 6 months ± 30
Administrative Procedures																	
Informed consent	x																
Inclusion/exclusion criteria	x																
Demographics and medical history[15]	x																
Registration	x																
Prior and concomitant medication review	x[16]		x	x	x		x	x	x	x	x	x	x	x			
Trial treatment administration			x	x	x	x	x	x	x	x	x	x	x				
Drug compliance review				x			x	x	x	x	x	x	x	x			
Post-study anti-cancer therapy status														x	x	x	x
Survival status																	x
Clinical Procedures/Assessments																	
Review adverse events				x	x		x	x	x	x	x	x	x	x	x		
Physical examination[3]	x		x	x	x		x	x	x	x	x	x	x	x			
Vital signs[14], weight and height (screening only)	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			
Laboratory Procedures/Assessments[8]																	
Pregnancy test – urine or serum β -HCG		x[4]			x[4]									x[4]			
Coagulation (PT/INR and aPTT)		x															
Hematology (CBC with differential)[17]		x	x	x	x	x	x	x	x	x	x	x	x	x			
Comprehensive serum chemistry panel[19]		x	x	x	x		x	x	x	x	x	x	x	x			
Urinalysis[18]		x		x			x		x		x		x	x			
Thyroid functioning[20, 25]		x		x			x		x		x		x	x			
HgbA1c[11]		x	x	x	x		x	x	x	x	x	x	x				

Response Assessment																
Tumor imaging - CT (chest, ab, pelvis)	x							x 13			x[24]			X[23]		x[5]	
Tumor imaging - bone scan	x							x 12 , 13			x[12]			x[12]			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																	
Archival (when available) or newly obtained tissue collection (optional)	x[6]					x[6]											
Correlative studies blood collection (PD)[22]	x		x[7]		x		x		x		x		x	x[9]			

Footnotes:

[1] If the subject discontinues treatment due to disease progression, a phone call to the patient can serve as the safety follow-up visit if the end of treatment visit was done. If a subject initiates a new anti-cancer therapy within 90 days after the last dose of trial treatment, the subject will move into survival follow-up.

[2] Applies to subjects who discontinue trial treatment for a reason other than disease progression. Subjects should be assessed per institutional guidelines by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment.

[3] A complete physical examination will be performed during the screening phase and at the treatment discontinuation visit and should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.
A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

[4] If a female of childbearing potential, must have a negative serum blood pregnancy test during screening and a negative urine pregnancy test within 3 days prior to receiving the first dose of study drug. If the screening serum test is done within 3 days prior to receiving the first dose of study drug, a urine test is not required.

[5] After 1 year, image every 6 months ± 2 weeks

[6] Whenever available, archival tissue from a metastatic lesion will be obtained at screening. If archival tissue is unavailable, patients will be given the option to consent to a biopsy during the screening phase (applies to run-in and combination phases) and a second biopsy on Cycle 1 Day 14 (+/- 3 days) during the combination phase.

[7] Run-in Phase, Cycle -2 Day 1 and 14

[8] After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

[9] When patients are taken off treatment and at the time of disease progression blood for correlative markers will be also obtained.

[10] -28 days for patients in the run-in phase; -71 to -43 days for patients on the combination phase.

[11] HcbA1c labs are only required for patients with pre-existing condition of diabetes mellitus.

[12] Only as clinically indicated with a window of +/- 7 days

[13] Imaging will be done prior to the dosing on C3D1. with a window of - 7 days

[14] Heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[15] Includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), and prior cancer therapies and procedures

[16] All medications used within 10 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies)

[17] CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count

[18] Specific gravity, pH, glucose, protein (creatinine [UPC] ratio or dipstick), ketones, and blood

[19] Glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, and amylase/lipase (amylase/lipase only done at screening)
[20] TSH, free T3, and free T4 tests are mandatory.
[21] The Run-In Phase will only be done during Phase II. The Run-In Phase may be skipped at the treating physician's discretion for patients in Cohort A
[22] Blood samples should be collected prior to treatment administration whenever possible.
[23] Tumor assessments only required if clinically indicated with a window of +/- 7 days
[24] Tumor imaging - CT (chest, ab, pelvis) every 3 cycles (repeated) after cycle 6 (i.e. cycle 9,12,15,18,etc.) with a window of +/- 7 days
[25] Epstein-Barr virus (EBV) serology (EBNA IgG), hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated. HBV DNA test is required for patients who have known positive serology for anti-HBc. HCV RNA test is required for patients who have known positive serology for anti-HCV.

Appendix 2 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \cdot \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \cdot 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \cdot (140\text{-Age}) \cdot \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \cdot 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

Appendix 3 Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Classification and grading: Classification and grading of adverse event will utilize the National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) version 4.0 to determine the severity of the reaction for adverse event reporting.

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST)

Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a. Measurable Tumor 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 of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ε 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ε 10 to < 15 mm short axis), 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 masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure 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 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) since 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 subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of 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.

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

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ε 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 is preferred over chest X-ray, particularly when progression is an important endpoint, since 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, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 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 intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT 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 is done, the decision as to whether non-contrast CT 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 radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

<u>Tumor Response Evaluation</u>
Assessment of Overall Tumor Burden and Measurable Disease
To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, 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.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, 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 x 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 <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

<u>All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”</u>

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

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

The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis <10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure 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 BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since 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 BML should also be ticked.)

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. 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 maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be

measured and, instead, should be assessed only qualitatively at the time points specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)

All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

<u>A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.</u>

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Response

a. Time point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. **Table 1** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, **Table 2** is to be used.

Table 1. Time point Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2. Time point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. 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 only a subset of lesion measurements are made at an assessment, 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 lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline 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 PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that time point (**Table 3**).

Table 3. Best Overall Response When Confirmation Is Required

Overall Response at First Time point	Overall Response at Subsequent Time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression 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 disease as shown in **Tables 1 – 3**.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5 Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[3] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

[3] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412□20.

GLOSSARY

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

BASELINE ASSESSMENT USING irRC

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

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

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

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

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

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

Step 4. Calculate the tumor burden:

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

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

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

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥4 weeks from the date first documented
irPR	Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment ε4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥25% relative to nadir confirmed by a consecutive assessment ≥4 weeks from the date first documented

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

DETERMINATION OF irBOR

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

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

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

Appendix 6 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 7 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 drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. 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 observation.

Appendix 8 Safety Reporting Fax Cover Sheet

Genentech
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GENENTECH SUPPORTED RESEARCH

AE/SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-4630

Page 1 of ___

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/__/__ dd / mmm / yyyy
Follow-up Report Date	_____/__/__ dd / mmm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	____ - ____ -____

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

Appendix 9 FDA MedWatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email.

Appendix 10 Trial medication Diary (entinostat)

See attached PDF version 6/2/2017.