UCSF Helen Diller Family Comprehensive Cancer Center

Phase II Study of Neoadjuvant Atezolizumab-based Immunotherapy for Patients with Urothelial Carcinoma (NEBULA)

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Protocol Signature Page

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data and Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.
3. I certify that I, and the study staff, have received the required training to conduct this research protocol.
4. I agree to maintain adequate and accurate records in accordance with IRB policies, federal, state and local laws and regulations.

UCSF Principal Investigator

_____
Printed Name

_____ _____
Signature Date

Protocol Signature Page – Participating Sites

Participating Site(s)

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[redacted]

I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP) and the applicable IRB, ethical, federal, state, and local regulatory requirements.

***Instructions to the investigator**: Please **SIGN** and **DATE** this signature page. **PRINT** your name and the name of the facility in which the study will be conducted. Scan and email the completed form to UCSF Helen Diller Family Comprehensive Cancer Center and keep a record for your files.*

Signature of Principal Investigator

Date

Name of Principal Investigator (Printed)

Name of Facility

Abstract

Title	Phase II Study of Neoadjuvant Atezolizumab-based Immunotherapy for Patients with Urothelial Carcinoma (NEBULA)
Phase of Study	Phase II
Study Drugs	Atezolizumab, an anti-PD-L1 antibody. Dose will be 1200mg IV given on Day 1 of a 21-day cycle x 3 doses. Tiragolumab, an anti-TIGIT antibody (Cohort B only). Dose will be 600mg IV on Day 1 of a 21-day cycle x for up to 3 doses
Study Population	Subjects with muscle-invasive urothelial cell carcinoma of the bladder
Study Design	This is a single arm, open label multiple-cohort phase II study of atezolizumab, an anti-PD-L1 antibody, alone or in combination with tiragolumab, an anti-TIGIT antibody, administered as neoadjuvant therapy to patients with muscle-invasive urothelial carcinoma appropriate for cystectomy and either refusing or ineligible for neoadjuvant cisplatin-based chemotherapy. Enrolled patients will receive atezolizumab (1200mg IV on Day 1 of a 21 day cycle) and, in the combination cohort, tiragolumab (600mg IV on Day 1 of a 21 day cycle) as neoadjuvant treatment for an intended total of three treatment cycles. As of October 2020 the atezolizumab monotherapy cohort (Cohort A) has completed dose escalation and is in dose expansion, and will accrue up to 27 total patients. Once amendment 4.3 (October 19th, 2020) is approved patients will only be accrued to the combination cohort (Cohort B). For Cohort B there will be an initial safety lead in phase for combination treatment, detailed in Section 3.1. Once the intended treatment regimen is established following completion of the safety assessment, an additional 15 patients will be enrolled at the same regimen for a total of 21 patients in Cohort B at the established regimen. Consequently, a minimum of 21 and a maximum of 33 patients will be enrolled in Cohort B. After all neoadjuvant study therapy is administered, each patient will undergo radical cystectomy with pelvic lymph node dissection to evaluate pathologic response to treatment and for immunologic characterization in the resected tissue. All patients will undergo radical cystectomy within 12 weeks of the start of neoadjuvant treatment. Any delays in surgery beyond 12 weeks from the start of neoadjuvant treatment that are thought to be treatment related will be considered an adverse event. Serum and urine will be obtained as well to characterize circulating immune

	responses. Following completion of radical cystectomy all patients will be followed clinically for up to 2 years with regular visits and imaging to assess for disease recurrence.
Primary Objectives	**Cohort A (Atezolizumab Monotherapy):** Multi-dose cohorts: To assess the intratumoral immune response associated with increasing numbers of Atezolizumab treatments. Expansion cohort: To assess the anti-tumor activity of Atezolizumab as determined by the pathologic T0 rate (pT0N0) at the time of cystectomy. **Cohort B (Atezolizumab + Tiragolumab):** Multi-dose cohorts: To assess the safety of neoadjuvant combination treatment with atezolizumab and tiragolumab according to CTCAE v5.0 in cisplatin-ineligible patients with MIBC undergoing radical cystectomy. Expansion cohort: To assess the anti-tumor activity of Atezolizumab + Tiragolumab as determined by the pathologic T0 rate (pT0N0) at the time of cystectomy.
Secondary Objectives	**Cohorts A & B** Multi-dose cohorts: 1. To evaluate the safety and feasibility of administering up to 3 cycles of Atezolizumab pre-operatively to patients with resectable urothelial bladder cancer. Note this is the coprimary objective for Cohort B. Expansion cohort: 1. To assess the anti-tumor activity of neoadjuvant treatment as determined by pathologic pathologic partial response (<pT2N0) assessed at the time of radical cystectomy 2. To determine the 2-year relapse-free survival (RFS) rate and median RFS from time of radical cystectomy in patients treated with neoadjuvant therapy 3. To determine the 2-year overall survival (OS) and median OS from time of radical cystectomy in patients treated with neoadjuvant therapy

	4. To assess the intratumoral immune response of neoadjuvant by comparing pre-treatment TURBT with post-treatment cystectomy tumor specimens
Exploratory Objectives	**Cohorts A & B** 1. To define the immunologic infiltration within bladder tissue following administration of neoadjuvant combination treatment with atezolizumab and tiragolumab when compared to pre-treatment TURBT biopsies 2. To assess the immunologic impact of combined tiragolumab and atezolizumab regimen in the urothelial cancer tumor microenvironment (Cohort B) in comparison to the impact on the tumor microenvironment of atezolizumab monotherapy in a similar cohort of patients treated with neoadjuvant atezolizumab for MIBC at UCSF (Cohort A) 3. To assess for tumor-based biomarkers of response and resistance to this combination therapy using single-cell RNA sequencing (scRNA-seq) and high-dimensional flow cytometry 4. To define the treatment-induced effects on circulating immune cells with this combination therapy 5. To assess the presence of antigen-specific immune responses to a broad panel of candidate tumor antigens
Sample Size	Cohort A Safety Lead-In: 18 participants (already accrued as of October 2020) Cohort A Expansion: Up to 9 additional participants may be accrued so that Cohort A expansion group = up to 15 total participants treated at established regimen (6 participants treated at highest administered dose from multi-dose portion + up to 9 additional participants). Cohort B Safety Lead-In: 6-18 patients will be included. Cohort B Expansion: 15 additional patients treated with the regimen established during the safety lead-in phase (21 total treated with established regimen) Total Cohort A accrual: Up to 27 patients Total Cohort B accrual: 21-33 patients
Duration of Study Treatment	9 weeks

Duration of Follow up	2 years
Safety Assessments	For Cohort A: Frequency of all grade treatment-related toxicities according to NCI CTCAE v4.0 For Cohort B: Frequency of all grade treatment-related toxicities according to NCI CTCAE v5.0
Efficacy Assessments	Pathologic complete response rate (pT0N0), pathologic partial response rate (<pT2N0), median relapse-free survival and overall survival, 2 year relapse-free survival rate and overall survival rate
Unique Aspects of this Study	This is the first study to evaluate the safety and efficacy of atezolizumab-based neoadjuvant therapy prior to radical cystectomy in patients with muscle-invasive urothelial carcinoma who are either ineligible for or refusing cisplatin-based chemotherapy. Similarly it is the first study to provide a comprehensive characterization of the immunologic effects in the bladder tumor microenvironment of the neoadjuvant atezolizumab-based regimen prior to radical cystectomy.

1 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CHO	Chinese hamster ovary
CI	Confidence interval
CIS	carcinoma in situ
CK	creatine kinase
CR	complete response
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EBV	Epstein-Barr virus
ECG/EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Conference on Harmonization
IRR	infusion-related reaction
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
ITT	intent-to-treat
LDH	lactate dehydrogenase
LFT	liver function test
MIBC	muscle-invasive bladder cancer
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NK	natural killer
ORR	overall response rate
pCR	pathologic complete response
PD	disease progression
PD-1	programmed death-1 receptor
PD-L1	programmed death-1 ligand
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRC	Protocol Review Committee (UCSF)
PVR	poliovirus receptor
RFS	relapse-free survival
SD	stable disease
TBNK	T, B, and NK cells
TCC	transitional cell carcinoma
TIGIT	T cell immunoreceptor with Ig and ITIM domains
TSH	thyroid-stimulating hormone
UC	urothelial cancer
ULN	upper limit of normal

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1 Introduction

1.1 Background on Bladder Cancer

Urothelial cancer (UC) is the most common cancer of the urinary system worldwide with transitional cell carcinoma (TCC) being the predominant histologic type. It was estimated that in 2013, there would be 72,570 new cases of bladder cancer and 15,210 deaths in the United States.[1] Non-muscle invasive disease (stages Ta, T1, or carcinoma in situ (CIS)) accounts for approximately half of new diagnoses, muscle-invasive disease (stages T2-4) accounts for approximately 35% of new diagnoses, and metastatic disease accounts for the remainder. When confined to the bladder itself UC is a curable disease, although treatment approaches differ depending on the presence of muscle invasion as discussed below.

1.2 Treatment of Muscle Invasive Bladder Cancer (MIBC)

Although bladder tumors that are non-muscle invasive are treated with intravesical treatments such as BCG; due to the depth of invasion, intravesical treatments are inadequate for patients with muscle-invasive disease. Therefore, more definitive therapy is needed. Although concurrent chemoradiation may be used for patients who are not surgical candidates or for those desiring bladder preservation, radical cystectomy and bilateral pelvic lymphadenectomy is considered the standard of care. The addition of neoadjuvant cisplatin-based chemotherapy has been associated with both improved overall survival as well as a lower risk of recurrence.[2] This was illustrated in a randomized Phase III study in which 3 cycles of neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy increased the pathologic T0 rate from 15% to 38% ($p<0.001$) and was associated with a trend toward increased median survival (46 vs. 77 months, $p=0.06$) when compared to surgery alone.[3] Importantly, in this study a pathologic complete response (pCR) to neoadjuvant therapy was associated with both a disease-free and an overall- survival benefit, suggesting that downstaging tumors prior to surgery may confer long term benefit. An analysis of 11 randomized trials of cisplatin-based neoadjuvant chemotherapy concluded neoadjuvant therapy confers a modest survival benefit (OS, hazard ratio [HR] for mortality 0.87, 95% CI 0.78-0.98) corresponding to an absolute survival benefit of 5%, and a modest reduction in the risk of recurrence (HR for recurrence 0.81, 95% CI 0.74- 0.90), corresponding to an absolute disease-free survival benefit of 7%.[2]

Despite these benefits associated with chemotherapy prior to cystectomy, nationally less than 20% of patients undergoing radical cystectomy for MIBC actually receive neoadjuvant therapy.[4, 5] Among concerns include advanced patient age, comorbidities, concerns over chemotherapy toxicity, and the modest nature of benefit from chemotherapy.[6] Similarly there is no neoadjuvant standard of care for patients with marginal renal function, advanced hearing loss, or significant peripheral neuropathy that makes them ineligible for cisplatin therapy. Therefore, novel approaches for these patients are needed.

1.3 PD-L1 Immune Checkpoint Blockade

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit, and in recent years immunotherapeutic have been approved for multiple solid tumors including prostate cancer and melanoma.[7-9]

PD-L1 is an extracellular protein expressed on multiple tissues that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T-cells following T-cell activation, which is

sustained in states of chronic stimulation such as in chronic infection or cancer.[10, 11] Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production.[12, 13]

In cancer PD-L1 expression is prevalent in many human tumors, and overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion.[10] In UC elevated PD-L1 expression on tumor cells is associated with a increased pathologic stage, and PD-L1 expression predicts all causes-mortality after cystectomy for patients with organ-confined tumors.[14, 15]

1.4 Background on Atezolizumab

Atezolizumab is a human immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. It targets programmed death-ligand 1 (PD-L1) on antigen-presenting cells or tumor cells and prevents interaction with programmed death−1 (PD-1) receptor, which is an inhibitory receptor expressed on T cells. Atezolizumab also blocks the interaction between PD-L1 and B7.1. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function.

Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc‑effector function.

1.4.1 Non-Clinical Pharmacokinetics and Metabolism and Toxicology

The pharmacology, pharmacokinetics, and toxicology of atezolizumab have been investigated in several nonclinical studies. Atezolizumab binds to recombinant human and murine PD-L1 with subnanomolar affinity (Kd = 0.433 nM and 0.134 nM, respectively) and with comparable affinity to PD-L1 on cynomolgus monkey (*Macaca fascicularis*) T cells (50% effective concentration [EC50] = 0.704 nM). Atezolizumab does not induce cytokine release from human peripheral blood mononuclear cells (PBMCs) following in vitro culture with immobilized or soluble atezolizumab. Two chimeric derivatives of atezolizumab (PRO304397, PRO314483) were generated to assess efficacy in mouse models with minimal interference of murine antibodies directed to human IgG.

Studies were conducted to assess the potential of PD-L1 blockade to enhance anti-tumor immunity when administered to mice with established tumors of colorectal and melanoma origin in three different genetic strains of mice. Anti−PD-L1 induced complete regression of immunogenic MC38 colorectal tumors and up to 60% overall responses in mice with unmodified established MC38 tumors. Tumor growth inhibition rates from 76% to 119% were observed and time to progression was increased by 1.75- to 3-fold in response to anti−PD-L1. Therefore, blockade of PD-L1 represents a compelling strategy for enhancing anti-tumor T-cell responses for the treatment of solid tumors.

In addition to the nonclinical tumor efficacy studies described above, the activity of anti−PD-L1 was also evaluated in mouse infection models. Initial in vivo studies assessed the efficacy of atezolizumab in mice infected with lymphocytic choriomeningitis virus (LCMV). When anti−PD-

L1 was administered during the chronic phase of LCMV CL-13 infection, the antibody was effective in enhancing T-cell function and reducing viral load without evidence of toxicity. However, blockade of PD-L1 at the peak of the acute T-cell response and concomitant peak viremia following LCMV CL-13 infection resulted in a mortality rate of 80%−100%. Published and internal data show that these mortalities are not unique to this molecule or pathway since similar mortalities are observed in this model with other PD-1 and PD-L1 inhibitors, as well as with IL-2[16]. Rather, the data suggest that the mortalities observed in the acute CL-13 infection model are mediated by enhanced $CD8^+$ T-cell function in the presence of extremely high viral burden in multiple organs thereby compromising vascular integrity leading to circulatory system collapse.[17] The unique features of the murine CL-13 infection model contribute significantly to these deaths, and these features are not representative of the vast majority of viral infections that affect humans.

1.4.2 Toxicology and Safety Pharmacology

The toxicology program was designed to support clinical administration of Atezolizumab for up to 2 months when administered intravenously or subcutaneously to patients and consisted of the following:

- A 15-day pilot study in mice
- An 8-week repeat-dose study in cynomolgus monkeys
- An in vitro hemolytic potential assay
- A tissue cross-reactivity analysis of human and cynomolgus monkey tissues.

The mouse was considered the preferred rodent species in which to test the toxicity of Atezolizumab because the PD-L1/PD-1 pathway has been characterized more extensively in mice than in rats. The nonclinical efficacy studies were conducted in mice, as the known biology is more comparable to that in humans. Additionally, the availability of murine- specific reagents enabled an extensive immune response characterization. The pilot study demonstrated a high level of immunogenicity in mice. The immune response to Atezolizumab resulted in rapid drug clearance in a pilot mouse study in C57BL/6 and CD-1 mice, which would confound interpretation of immune system consequences of blocking PD-L1/PD-1 in a study of longer than 2 weeks; thus, the use of this species was precluded in studies of > 2 weeks for assessment of general toxicity. Because Atezolizumab binds to PD-L1 in cynomolgus monkeys and humans with comparable affinity, the cynomolgus monkey was chosen as the most appropriate species to assess the systemic toxicity of Atezolizumab. At necropsy, arteritis was observed in 3 animals at the 50 mg/kg dose and 1 animal at the 15 mg/kg dose. These histological findings were not associated with any clinical signs or symptoms. As no arteritis was found in animals treated with 5 mg/kg, this dose level was identified as the NOAEL. All other findings were considered incidental and not drug related. Overall, Atezolizumab was clinically well tolerated by cynomolgus monkeys at doses up to 50 mg/kg for 8 weeks (total of nine doses) (Study 08-1148).

The Phase I starting dose of 0.01 mg/kg was based on nonclinical PK/PD data that projected ~80% receptor occupancy at the Cmax of this dose (unpublished data) and was supported by the toxicology data. On the basis of this starting dose, a safety factor of 160-fold based on BSA was determined as it relates to the NOAEL of 5 mg/kg in the 8-week, repeat dose GLP toxicity study in cynomolgus monkeys.

1.5 Clinical Studies of Atezolizumab

There are multiple ongoing studies of Atezolizumab, and it has received accelerated FDA approval for the treatment of urothelial cancer. Details of all studies may be found in the Atezolizumab Investigator's Brochure (IB). Briefly, in patients with metastatic disease, the IMvigor 210 study[18] enrolled 310 subjects with inoperable locally advanced or metastatic urothelial carcinoma whose disease had progressed after previous platinum-based chemotherapy. These patients received atezolizumab 1200mg IV every 3 weeks. The PD-L1 expression status on infiltrating immune cells (ICs) in the tumor microenvironment was defined by the percentage of PD-L1-positive immune cells: IC0 (<1%), IC1 (≥1% but <5%), and IC2/3 (≥5%). The primary analysis showed that compared with a historical control overall response rate of 10%, treatment with atezolizumab resulted in a significantly improved RECIST v1.1 objective response rate for each prespecified immune cell group (IC2/3: 27% [95% CI 19–37], p<0·0001; IC1/2/3: 18% [13–24], p=0·0004) and in all patients (15% [11–20], p=0·0058). With longer follow-up (data cutoff Sept 14, 2015), by independent review, objective response rates were 26% (95% CI 18–36) in the IC2/3 group, 18% (13–24) in the IC1/2/3 group, and 15% (11–19) overall in all 310 patients. With a median follow-up of 11.7 months (95% CI 11·4–12·2), ongoing responses were recorded in 38 (84%) of 45 responders. Exploratory analyses showed The Cancer Genome Atlas (TCGA) subtypes and mutation load to be independently predictive for response to atezolizumab. Grade 3–4 treatment-related adverse events, of which fatigue was the most common (five patients [2%]), occurred in 50 (16%) of 310 treated patients. Grade 3–4 immune-mediated adverse events occurred in 15 (5%) of 310 treated patients, with pneumonitis, increased aspartate aminotransferase, increased alanine aminotransferase, rash, and dyspnea being the most common. No treatment-related deaths occurred during the study. Similar studies including IMvigor 211 and SAUL have demonstrated comparable results.

In the neoadjuvant setting one study in addition to this trial explored the value of atezolizumab as monotherapy. The ABACUS study[19] was an open-label, international, multicenter, single-arm, neoadjuvant phase 2 trial evaluating the effects of two cycles (1,200 mg, three times weekly) of preoperative atezolizumab in patients with histologically confirmed (T2–T4aN0M0) transitional cell UC of the bladder, awaiting planned radical cystectomy. Additional eligibility criteria included residual disease after TURBT, adequate fitness for planned cystectomy (according to local guidelines), ineligibility for or refusal of cisplatin-based neoadjuvant chemotherapy, no evidence of nodal or metastatic disease on cross-sectional imaging, ECOG performance status of 0 or 1, and adequate hematologic and end-organ function within 4 weeks of the first study treatment. Major exclusion criteria included evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, previous autoimmune disease, ongoing active infections or prior use of immune checkpoint inhibitors. Pathological complete response was the primary endpoint. Secondary endpoints focused on safety, relapse-free survival and biomarker analysis. The pathological complete response rate was 31% (95% confidence interval: 21–41%). Baseline biomarkers showed that the presence of preexisting activated T cells was more prominent than expected and correlated with outcome. Other established biomarkers, such as tumor mutational burden, did not predict outcome, differentiating this from the metastatic setting. Dynamic changes to gene expression signatures and protein biomarkers occurred with therapy, whereas changes in DNA alterations with treatment were uncommon. Responding tumors showed predominant expression of genes related to tissue repair after treatment, making tumor biomarker interpretation challenging in this group. Stromal factors such as transforming growth factor-β and fibroblast activation protein were linked to resistance, as was high expression of cell cycle gene signatures after treatment.

A similarly designed study, the PURE-01 trial[20], also accrued patients with MIBC to receive neoadjuvant PD-1 checkpoint inhibition. Patients had a predominant urothelial carcinoma histology and clinical (c)T≤3bN0 stage tumor. They received three cycles of pembrolizumab (a PD-1 inhibitor) 200 mg every 3 weeks before RC. The primary end point in the intention-to-treat population was pathologic complete response (pT0). Biomarker analyses included programmed death-ligand 1 (PD-L1) expression using the combined positive score (CPS; Dako 22C3 pharmDx assay), genomic sequencing, and an immune gene expression assay. Fifty patients were enrolled from February 2017 to March 2018. Twenty-seven patients (54%) had cT3 tumor, 21 (42%) cT2 tumor, and two (4%) cT2-3N1 tumor. One patient (2%) experienced a grade 3 transaminase increase and discontinued pembrolizumab. All patients underwent RC; there were 21 patients with pT0 (42%; 95% CI, 28.2% to 56.8%). As a secondary end point, downstaging to <pT2 was achieved in 27 patients (54%; 95% CI, 39.3% to 68.2%). In 54.3% of patients with PD-L1 CPS ≥ 10% (n = 35), RC indicated pT0, whereas RC indicated pT0 in only 13.3% of those with CPS < 10% (n = 15). A significant nonlinear association between tumor mutation burden (TMB) and pT0 was observed, with a cutoff at 15 mutations/Mb. Expression of several genes in pretherapy lesions was significantly different between pT0 and non-pT0 cohorts. Significant post-therapy changes in the TMB and evidence of adaptive mechanisms of immune resistance were observed in residual tumors.

1.6 Background and Clinical Studies of Tiragolumab

Tiragolumab is a fully human immunoglobulin G1 (IgG1)/kappa mAb derived in Open Monoclonal Technology (OMT) rats that binds T-cell Immunoreceptor with Immunoglobulin and Immunoreceptor Tyrosine-Based Inhibition Motif [ITIM] domains (TIGIT) and prevents its interaction with the poliovirus receptor (PVR). The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each).

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. TIGIT is an immunoglobulin (Ig) super family member expressed on subsets of activated T cells and natural killer (NK) cells, and found highly expressed in tumor tissue and in tumor-infiltrating immune cells in many human cancers, including, but not limited to NSCLC, breast cancer, multiple myeloma, and non-Hodgkin lymphoma. In multiple tumor types, TIGIT is coordinately expressed with PD-1[21-23]. Genetic ablation or antibody blockade of TIGIT has been shown to enhance NK cell killing, CD4+ and CD8+ T-cell activation, and effector function in vitro and in vivo in nonclinical models.[21, 22, 24, 25] In the nonclinical tumor models, TIGIT interacted with high affinity to CD155 (also known as PVR), which also has an activating counter-receptor CD226. Activation of TIGIT on T cells and NK cells was demonstrated to limit proliferation, effector cytokine production, and killing of target tumor cells.[21, 22, 24]

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients. Refer to the tiragolumab Investigator's Brochure for details on nonclinical studies.

Clinically study GO30103[26] is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with

atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including urothelial cancer, renal cell cancer, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, colorectal cancer (CRC), gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the data cutoff date of 3 December 2018, 42 patients had received tiragolumab monotherapy at doses of 2−1200 mg, and 164 patients had received tiragolumab at doses of 2−600 mg in combination with 1200-mg atezolizumab. The best observed response with tiragolumab monotherapy was prolonged stable disease in 8 of 42 patients, with some patients (including 1 patient with CRC) experiencing a decrease in tumor size. Among 164 patients receiving tiragolumab in combination with atezolizumab, a complete response was observed in 3 patients (including 1 patient with esophageal cancer), a partial response was observed in 22 patients (including patients with esophageal cancer), and stable disease was observed in 38 patients. Among 4 patients with urothelial cancer receiving tiragolumab in combination with atezolizumab, a confirmed partial response was observed in 3 patients.

No maximum tolerated dose, dose-limiting toxicities (DLTs), or clear dose-related trends in the incidence or severity of adverse events have been determined for tiragolumab as a single agent or in combination with atezolizumab. A fatal case of hepatic toxicity culminating in fulminant liver failure occurred in a patient with metastatic head and neck cancer receiving single-agent tiragolumab at the highest dose cleared for enrollment (1200 mg) (see the tiragolumab IB for details). No other fatal cases of fulminant liver failure have been observed.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile is observed to be consistent across different solid tumor indications.

A second study GO40290[27] is a global, multicenter, randomized, blinded, placebo-controlled Phase II study designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced unresectable, or metastatic PD-L1−selected NSCLC.

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS ≥ 1% were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab (n = 67) or placebo plus atezolizumab (n = 68). Of the enrolled patients, 43.0% of patients had a TPS ≥ 50% relative to 57.0% of patients with a TPS 1%−49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never- smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

In the ITT population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%). In the subgroup of patients with TPS ≥ 50%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n = 29; 55.2% [95% CI: 35.4%, 75.0%]) than the placebo plus atezolizumab arm (n = 29; 17.2% [95% CI: 1.8%, 32.7%]). Of note, responders in the tiragolumab plus atezolizumab arm included patients with both squamous and non-squamous histology.

In the ITT population, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (stratified HR =□0.57 [95% CI: 0.37, 0.90]; median PFS 5.4 vs. 3.6 months, respectively). In the subgroup of patients with TPS ≥ 50%, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified HR = 0.33 [95% CI: 0.15, 0.72]; median PFS not estimable (NE) vs. 3.9 months, respectively) (Roche unpublished data on file).

To date, most adverse events have been Grade 1 or Grade 2. Serious adverse events, Grade 3–5 adverse events, adverse events leading to discontinuation, and adverse events leading to death have been balanced between the two treatment arms. Serious and high-grade treatment-related adverse events have also been balanced between the two treatment arms. Immune-mediated adverse events were balanced between the two treatment arms, with the exception of a higher frequency of infusion-related reaction and rash reported in the atezolizumab plus tiragolumab arm. Discontinuation due to adverse events was low (approximately 6% in both arms). A fatal case of Epstein-Barr virus (EBV) reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in Study GO40290 in a 69-year-old male in Taiwan with metastatic lymphoepithelioma-like carcinoma subtype of NSCLC (PD-L1 positive), which can be associated with EBV infection in Asian patients.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

1.7 Rationale for this Study

Based on the results of the ABACUS, PURE-01, CITYSCAPE trials and our unpublished data on clinical outcomes from the initial monotherapy treatment cohort, it appears that there is significant clinical activity of both of these agents, including indications of potential synergy, with acceptable risks. Given the need for novel therapies to improve outcomes for patients with MIBC ineligible for cisplatin-based chemotherapy, this study offers a potentially therapeutic option. It will additionally provide a wealth of correlative biologic and immunologic data to better understand the mechanism(s) by which these therapies work and identify prognostic and predictive biomarkers.

1.8 Rationale for the Study Design

This study will evaluate the pathologic and immunologic changes induced by atezolizumab-based therapy in bladder tissues compared to pretreatment biopsies. This study has two cohorts (Cohort A and Cohort B) and will accrue each cohort sequentially (i.e., Cohort A will fully accrue, then Cohort B).

Cohort A: Atezolizumab Monotherapy

In the initial monotherapy multi-dose phase (Cohort A), the effects of increasing numbers of doses of atezolizumab will be explored. Similarly, the safety, feasibility, and efficacy of administering up to 3 doses of atezolizumab in patients scheduled for cystectomy will also be examined.

- Multi-dose phase (fully accrued as of October 2020): A fixed number of 6 patients will be accrued at each dose level in the multi-dose portion of the study to allow for investigation into the immunologic impact of different cumulative doses of atezolizumab prior to cystectomy. It is unknown whether multiple doses of atezolizumab are necessary to achieve a complete response or a durable remission as opposed to a single dose, and accrual of 6 patients at each dose level will allow for a preliminary estimate of the efficacy of each cumulative dose level. The safety profile of atezolizumab is well established from multiple Phase I - III studies, and treatment related Grade 3 or 4 toxicities were rare. The multi- dose portion may better inform future studies of neoadjuvant atezolizumab and potentially allow for shorter neoadjuvant courses to be administered.
- Cohort A expansion phase opened after the multi-dose portion of Cohort A completed, consisting of up to 27 total patients in Cohort A. In order to reduce the number of subjects needed for this study and allow for faster study completion, the 6 subjects treated at the highest dose from the multi-dose phase of the study will be included as part of the expansion cohorts, therefore the total accrual to the expansion cohort after the multi-dose portion of Cohort A will be up to 9 subjects. The highest dose level is chosen for the expansion cohorts as it is expected that administration of multiple doses of atezolizumab will best enhance immune responses and lead to better clinical responses. These expansion cohorts will allow for a better estimate that treatment-related grade 3 or 4 events, or delays in cystectomy >12 weeks, are observed at a frequency of less than <33%. It will also allow for an exploratory estimation of efficacy of atezolizumab in this setting, and for further characterization of the immunologic effects of atezolizumab in this patient population.

Cohort B: Atezolizumab + Tiragolumab

After completion of enrollment into Cohort A, and upon approval of Amendment 4.3 (October 19, 2020) the study will begin accrual into Cohort B, where participants will receive combination neoadjuvant therapy with atezolizumab (1200mg IV on Day 1 of a 21 day cycle) and tiragolumab (600mg IV on Day 1 of a 21 day cycle) as neoadjuvant treatment for an intended total of three treatment cycles prior to an intended radical cystectomy. Similar to Cohort A, the safety and efficacy of administering up to 3 doses of atezolizumab in combination with tiragolumab preoperatively in patients scheduled for cystectomy will be examined. No adjuvant therapy will be offered as no study to date has shown benefit for adjuvant PD-1 therapy in urothelial cancer patients who had received prior immunotherapy.[28] Recently Checkmate-274 study had a press release indicating a DFS benefit for nivolumab over placebo for high-risk patients with urothelial cancer following radical cystectomy however none of these patients have had prior neoadjuvant immunotherapy.

- Safety Lead-in: As adding tiragolumab together with atezolizumab in patients with NSCLC generates only minimal additive toxicity, this study will start with an initial safety lead-in of 6 patients at which time enrollment will pause to assess the safety of this combination treatment. If dose limiting toxicities are met (certain AEs or surgery delay, as defined in Section 5.4) then fewer doses of tiragolumab will be evaluated (See **Cohort B Safety Lead-in Schema**).

- Expansion: Once the intended treatment regimen is established following completion of the safety assessment, an additional 15 patients will be enrolled at the same regimen for a total of 21 patients on that treatment regimen.

1.9 Correlative Studies

In addition to evaluating the change in immunologic infiltration in tumor tissues induced by study therapy, the safety, toxicity, and efficacy of neoadjuvant atezolizumab-based therapy, this study aims to more thoroughly characterize the immunologic response induced by treatment with study therapy.

More specifically, bladder tissue taken at the time of surgery and peripheral blood will be analyzed immunohistochemically and genomically in order to:

1. Characterize the tumor and immune cell subsets
2. Explore the location of tumor infiltration lymphocytes (e.g. within tumors, at tumor periphery)
3. Characterize T cell receptor diversity
4. Explore the correlation of tumor PD-L1 expression across different grades and stages of disease with response to therapy.

In addition, serum and blood will be analyzed to determine whether antigen-specific immune responses are modulated and to quantify and characterize circulating immune cell subsets.

2 Study Objectives

2.1 Primary Objectives and Endpoints

Cohort A (Atezolizumab monotherapy):

1. Multi-dose cohorts: To assess the intratumoral immune response associated with increasing numbers of Atezolizumab treatments.
    - Endpoint: CD3+ T cell count/μm2 between the pretreatment biopsy and the cystectomy tissue following single and multiple neoadjuvant Atezolizumab infusions.

2. Expansion cohort: To assess the anti-tumor activity of Atezolizumab as determined by the pathologic T0 rate (pT0N0) at the time of cystectomy.
    - Endpoint: Pathologic T0 rate at the time of cystectomy, defined as the pathologic absence of disease in the bladder after resection (See section 7.1.1).

Cohort B (Atezolizumab + tiragolumab)

1. To assess the safety of neoadjuvant combination treatment with atezolizumab and tiragolumab according to CTCAE v5.0 in a curative intent treatment population of urothelial carcinoma patients undergoing radical cystectomy.

    - Endpoint: The percentage of patients in Cohort B with treatment-related adverse events according to CTCAE v5.0 or treatment-related delays in surgery beyond 12 weeks following administration of neoadjuvant treatment with atezolizumab and tiragolumab.

2. To assess the anti-tumor activity of Atezolizumab + Tiragolumab as determined by the pathologic T0 rate (pT0N0) at the time of cystectomy.

    - Endpoint: Pathologic T0 rate at the time of cystectomy, defined as the pathologic absence of disease in the bladder after resection (See section 7.1.1).

2.2 Secondary Objective(s) and Endpoint(s)

Cohorts A and B

Multi-Dose Cohorts

1. To evaluate the safety and feasibility of administering up to 3 cycles of Atezolizumab pre-operatively to patients with resectable urothelial bladder cancer. Note this is the coprimary objective for Cohort B.

    - Endpoint: The percentage of patients with treatment-related adverse events according to CTCAE v5.0 or treatment-related delays in surgery beyond 12 weeks following administration of neoadjuvant treatment with atezolizumab with or without tiragolumab. Note for Cohort A CTCAE v4.0 was used.

Expansion Cohorts

1. To assess the anti-tumor activity of neoadjuvant treatment as determined by pathologic partial response (<pT2N0) assessed at the time of radical cystectomy

    - Endpoint: Percentage of patients with pathologic downstaging (<pT2N0) at the time of radical cystectomy

2. To determine the 2-year relapse-free survival (RFS) rate and median RFS from time of radical cystectomy in patients treated with neoadjuvant therapy

    - Endpoint: 2-year RFS rate and median RFS in ITT population

3. To determine the 2-year overall survival (OS) and median OS from time of radical cystectomy in patients treated with neoadjuvant therapy

    - Endpoint: 2-year OS rate and median OS in ITT population

4. To assess the intratumoral immune response of neoadjuvant by comparing pre-treatment TURBT with post-treatment cystectomy tumor specimens

- Endpoint: Association of tumor and T-cell PD-L1/PD-1 immunohistochemical expression with disease response

2.3 Exploratory (Correlative) Objectives

1. To define the immunologic infiltration within bladder tissue following administration of neoadjuvant combination treatment with atezolizumab and tiragolumab when compared to pre-treatment TURBT biopsies
2. To assess the immunologic impact of combined tiragolumab and atezolizumab regimen in the urothelial cancer tumor microenvironment (Cohort B) in comparison to the impact on the tumor microenvironment of atezolizumab monotherapy in a similar cohort of patients treated with neoadjuvant atezolizumab for MIBC at UCSF (Cohort A)
3. To assess for tumor-based biomarkers of response and resistance to this combination therapy using single-cell RNA sequencing (scRNA-seq) and high-dimensional flow cytometry
4. To define the treatment-induced effects on circulating immune cells with this combination therapy
5. To assess the presence of antigen-specific immune responses to a broad panel of candidate tumor antigens

Endpoints:

- Immunohistochemistry and gene expression analysis for immune cell subset quantification and localization within resected tumors, in particular through the comparison of intratumoral environment of post-treatment cystectomies to pre-treatment TURBTs
- Flow cytometry to evaluate changes in intratumoral and circulating immune cells
- T cell receptor (TCR) deep sequencing of tissue samples from pre-treatment biopsies and post-treatment resected tissues, and post-cystectomy circulating T cells.
- Immune response mRNA expression analysis to derive signatures associated with tumor response
- Identification of genomic mutations and gene copy aberrations associated with response and resistance to therapy
- Antigen array-base detection of circulating antibody responses
- Flow cytometry to evaluate changes in intratumoral and circulating immune cells
- T cell receptor (TCR) deep sequencing of tissue samples from pre-treatment biopsies and post-treatment resected tissues, and post-cystectomy circulating T cells.
- Immune response mRNA expression analysis to derive signatures associated with tumor response (expansion only)

- Identification of genomic mutations and gene copy aberrations associated with response and resistance to therapy (expansion only)
- Antigen array-base detection of circulating antibody responses (expansion only)

3 Study Design

3.1 Characteristics

This is a single arm, open-label multiple-cohort Phase II study of atezolizumab-based neoadjuvant therapy in subjects with muscle-invasive bladder cancer appropriate for cystectomy and refusing or ineligible for neoadjuvant cisplatin-based chemotherapy. This study has two cohorts (Cohort A and Cohort B) and will accrue each cohort sequentially (i.e., Cohort A will fully accrue, then Cohort B). Cohort A participants will receive neoadjuvant atezolizumab monotherapy and Cohort B participants will receive combination neoadjuvant treatment with atezolizumab and tiragolumab. As of October 2020, Cohort A has finished dose escalation and is in dose-expansion.

Following the administration of all intended neoadjuvant treatment regimen, participants will undergo cystectomy to evaluate pathologic response to treatment and for immunologic characterization in the resected tissue. Surgery should be performed within 12 weeks from the start of neoadjuvant treatment. Any treatment-related delays that put the surgery outside of this window will be considered an adverse event.

Serum and urine will be obtained as well to characterize circulating immune responses. Patients will be followed clinically for up to 2 years to assess for disease recurrence.

While adjuvant Atezolizumab was initially offered to patients in Cohort A who had pT3/pT4 or pN+ disease, given the lack of efficacy of adjuvant atezolizumab observed in the IMvigor 010 trial, no further adjuvant therapy will be offered to patients.

Cohort A (Atezolizumab monotherapy)

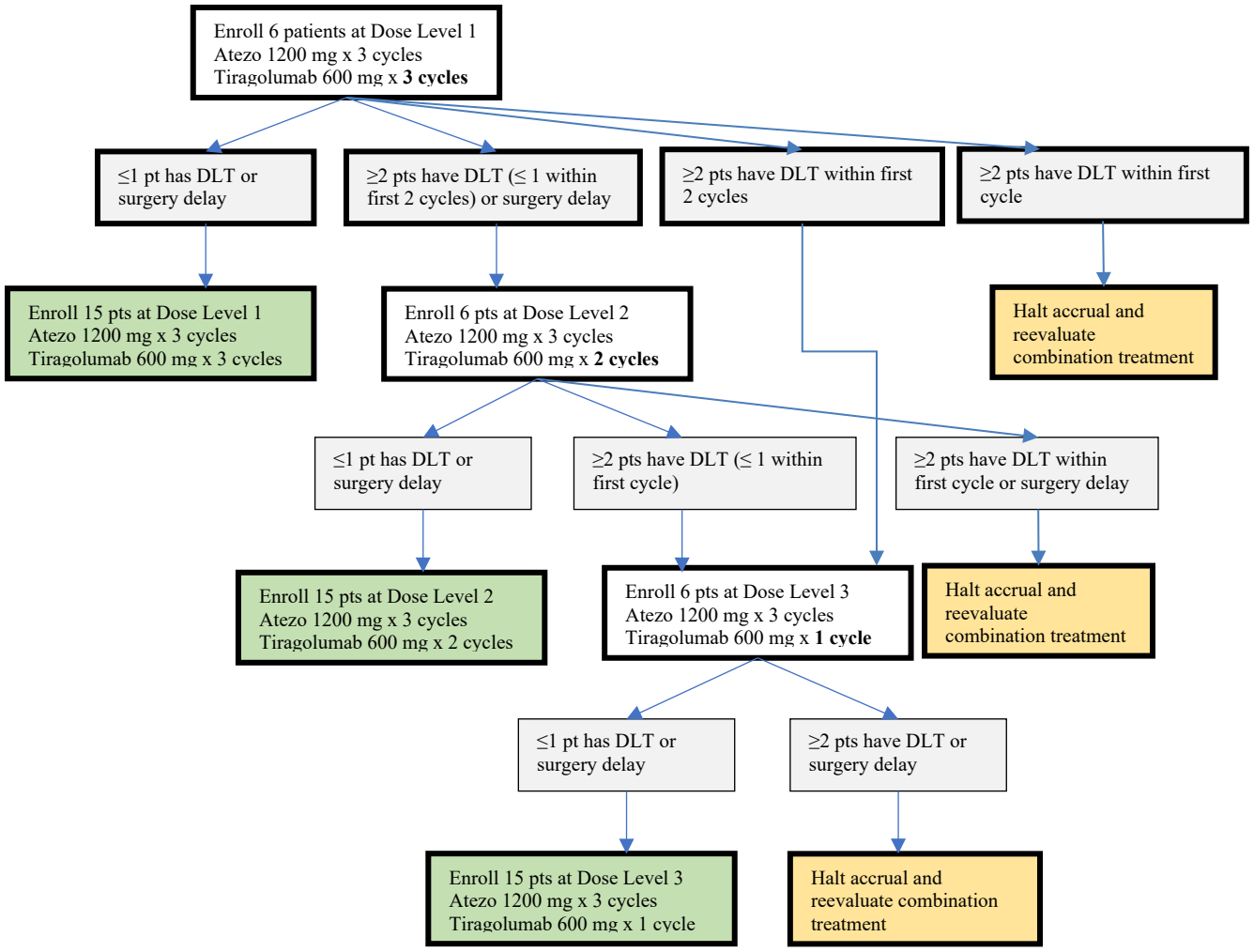
- Multi-dose phase (fully accrued): Enrolled patients will be assigned sequentially to atezolizumab dose levels in cohorts of 6 patients per dose level. The starting dose level is 1200mg x 1 dose and will be escalated in subsequent cohorts to 1200mg q 3 weeks x 2 doses, and finally 1200mg q 3 weeks x 3 doses.
- Expansion phase: After completion of the multi-dose phase, Cohort A expansion will open and up to 27 enrolled participants will receive atezolizumab 1200mg q 3 weeks x 3 doses prior to cystectomy.

Cohort B (Atezolizumab + tiragolumab)

After completion of Cohort A, Cohort B will open and enrolled patients will receive atezolizumab (1200mg IV on Day 1 of a 21 day cycle) and tiragolumab (600mg IV on Day 1 of a 21 day cycle) as neoadjuvant treatment for an intended total of three treatment cycles prior to an intended radical cystectomy.

- Safety Lead-in (see schema below):
    - **Dose Level 1** (Atezolizumab 1200 mg x 3 cycles, Tiragolumab 600 mg x 3 cycles): There will be an initial safety lead in of 6 patients treated with this regimen, at which time enrollment will pause to assess the safety of this combination treatment. As long as no more than 1 out of the initial 6 patients experience dose limiting toxicities (DLTs) or a delay in the time to radical cystectomy, the remaining patients will enroll at the same dose and regimen.
        - If two or more patients out of the initial six experience DLTs within the first cycle (3 weeks), accrual will be halted and the combination reevaluated.
        - If two or more patients out of the initial six experience DLTs within the first 2 cycles (6 weeks), accrual to this dose level will be halted and we will move to dose level 3.
        - If two or more patients out of the initial six experience DLTs or delay in the time to radical cystectomy, and no more than 1 patient experienced DLTs during the first 2 cycles (6 weeks), the next six patients will be treated at dose level 2
    - **Dose Level 2** (Atezolizumab 1200 mg x 3 cycles, Tiragolumab 600 mg x 2 cycles): As long as no more than 1 out of 6 patients experience DLTs or a delay in the time to radical cystectomy with this treatment, the remaining patients will enroll at the same dose and regimen.
        - If two or more patients out of the six patients experience DLTs within the first cycle (3 weeks), accrual will be halted and the combination reevaluated.
        - If two or more patients out of the six experience DLTs or delay in the time to radical cystectomy, and no more than 1 patient experienced DLTs during the first cycle (3 weeks), the next six patients will be treated at dose level 3
    - **Dose Level 3** (Atezolizumab 1200 mg x 3 cycles, Tiragolumab 600 mg x 1 cycle): This will be the selected regimen if no more than 1 out of 6 patients experience DLTs or a delay in the time to radical cystectomy. However if 2 or more patients experience DLTs or a delay in the time to radical cystectomy with this combination regimen, then accrual will be halted and the combination reevaluated.
- Expansion: Once the intended treatment regimen is established following completion of the safety assessment, an additional 15 patients will be enrolled at the same regimen for a total of 21 patients on that treatment regimen.

Cohort B Safety Lead-in Schema



3.2 Number of Participants

Total Cohort A accrual: Up to 27 participants

- Cohort A Safety Lead-In: 18 participants (already accrued as of October 2020)
- Cohort A Expansion: Up to 9 additional participants may be accrued so that Cohort A expansion group = up to 15 total participants treated at established regimen (6 participants treated at highest administered dose from multi-dose portion + up to 9 additional participants).

Total Cohort B accrual: 21-33 patients

- Cohort B Safety Lead-In: 6-18 patients will be included.
- Cohort B Expansion: 15 additional patients treated with the regimen established during the safety lead-in phase (21 total treated with established regimen)

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 18 years of age or older
2. ECOG performance status 0-1
3. Histologically documented transitional cell carcinoma with the presence of any of the following stages: grade cT2-T4a, considered appropriate for radical cystectomy. Subjects with mixed histology are required to have a dominant TCC pattern.
4. Patients not suitable for neoadjuvant cisplatin-based chemotherapy as determined by the following:
    a. Creatinine clearance less than 60ml/min. GFR should be assessed by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
    b. CTCAE Gr >/= 2 hearing loss
    c. CTCAE Gr >/= 2 neuropathy
5. Subjects with MIBC not meeting the above criteria are still eligible provided the patient declines neoadjuvant cisplatin-based chemotherapy, after specific informed consent describing the known benefits of cisplatin-based chemotherapy. The reason for declining must be documented.
6. Adequate bone marrow function defined as:
    a. WBC > 2500 cells/mm3
    b. ANC > 1500 cells/mm3
    c. Hemoglobin > 9 g/dL. Patients may be transfused or receive erythropoietic treatment to meet this criterion.
    d. Platelet count > 100,000 cells/mm3
7. Adequate renal function: Calculated CrCl > 30ml/min
8. Serum bilirubin < 1.5 x ULN (except for patients with documented Gilbert's disease)

9. AST and ALT < 2.5 x ULN

10. Ability to understand and willingness to sign a written informed consent.

11. Have available evaluable archival tumor tissue for PD-L1 biomarker assessment. Presence of PD-L1 antigen on tumors is NOT required for study entry.

12. The effects of atezolizumab or tiragolumab on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception prior to study entry, during study participation, and for 5 months after study treatment discontinuation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 90 days after completion of study drug administration.

3.3.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in this study:

1. Subjects with primary TCC of the ureter, urethra, or renal pelvis without TCC of the bladder are not allowed.

2. Known distant metastatic disease (e.g. pulmonary or hepatic metastases).

    a. Subjects with malignant lymphadenopathy in the abdomen or pelvis considered appropriate for radical cystectomy and lymphadenectomy with the goal of complete resection of all malignant disease are allowed.

3. Intravesical chemo- or biologic therapy within 6 weeks of first treatment.

4. Prior systemic chemotherapy, immunotherapy or radiation therapy for transitional cell carcinoma of the bladder.

    a. Subjects who have received prior intravesical chemotherapy or intravesical immunotherapy (e.g., interferon) are allowed.

5. Prior treatment with, anti-TIGIT antibodies, CD137 agonists or immune checkpoint blockade therapies, including anti CTLA-4, anti-PD1 and anti-PD-L1 therapeutic antibodies.

6. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegner's granulomatosis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vacuities, or glomerulonephritis.

    a. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

    b. Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study.

7. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.

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

8. HIV or active hepatitis B (HBV; chronic or acute; defined below) or active hepatitis C

    a. Patients with resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1, but detection of HBV DNA in these patients will not exclude study participation.

    b. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

9. Active tuberculosis

10. Positive Epstein-Barr virus (EBV) viral capsid antigen IgM test at screening
    a. An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded.

11. Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

12. Prior allogeneic stem cell or solid organ transplant

13. Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study. Inactivated vaccines (such as hepatitis A or polio vaccines) are permitted during the study.

    a. Influenza vaccination should be given during influenza season only (approximately September to March). Patients must not receive live attenuated influenza vaccine (e.g., FluMist) within 4 weeks prior to Cycle 1, Day 1 and for at least 12 weeks after the last dose.

14. Clinically significant active infection or uncontrolled medical condition based on the discretion of the treating physician

15. Uncontrolled cystitis, significant bladder pain or spasms, or gross hematuria that in the opinion of the treating investigator, should preclude study entry.

16. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina

    a. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

17. Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure other than cystectomy during the course of the study

18. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial

    a. Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Study Chair.

    b. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency) is allowed.

19. Pregnant or nursing women are excluded

20. Known hypersensitivity to Chinese hamster ovary (CHO) cell products or any component of the atezolizumab or tiragolumab formulation

21. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

22. Malignancies other than UC within 3 years prior to Cycle 1, Day 1, with the exception of those with a low risk of metastasis or death treated with expected curative outcome (such as, but not limited to, adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent and absence of PSA relapse, or ductal carcinoma in situ of the breast treated surgically with curative intent) or incidental prostate cancer (T1a, Gleason score ≤ 6 and PSA < 0.5 ng/mL).

3.4 Duration of Treatment

In the absence of treatment delays due to adverse events (AEs), neoadjuvant study treatment may continue (up to 3 cycles depending on cohort) until:

- Disease progression which requires discontinuation of the study treatment;
- Inter-current illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant decides to withdraw from the study;
- Significant participant non-compliance with protocol;
- If the participant meets an exclusion criterion (either newly developed or not previously; or, recognized) that precludes further study participation
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator.

3.5 Duration of Follow Up

Participants will be followed for 2 years after cystectomy, removal from study, or until death, whichever occurs first. Participants removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

3.6 Primary Completion

It is expected that the study will reach primary completion about 14-19 months from the time Cohort B opens to accrual, accounting for 11-16 months to accrue all subjects to Cohort B, and another 3 months from enrollment of last patient to cystectomy.

3.7 Study Completion

It is expected that the study will reach full completion 41-46 months from the time Cohort B opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage

4.1.1 Atezolizumab

Classification

Atezolizumab is a human monoclonal antibody based on a human IgG1 framework containing heavy chain VHIII and light chain Vκ I subgroup sequences. The recombinant antibody consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each) with inter- and intra-chain disulfide bonds that are typical of IgG1 antibodies.

Atezolizumab incorporates an amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of each heavy chain resulting in a non-glycosylated antibody that has minimal binding to Fcγ receptors and, consequently, prevents Fc-effector function and depletion of cells expressing PD-L1 at expected concentrations in humans. Therefore, atezolizumab lacks the N-linked oligosaccharides typically observed on other CHO-derived monoclonal antibodies.

Mechanism of Action

Atezolizumab targets programmed death-ligand 1 (PD-L1) on antigen-presenting cells or tumor cells and prevents interaction with programmed death−1 (PD-1) receptor, which is an inhibitory receptor expressed on T cells. Atezolizumab also blocks the interaction between PD-L1 and B7.1. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function.

Pharmacokinetics and Metabolism

Serum Atezolizumab concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase. Atezolizumab exhibited nonlinear pharmacokinetics at doses < 1 mg/kg (i.e., 0.03−0.3 mg/kg), likely due to target-mediated CL at lower concentrations. Atezolizumab exhibited linear pharmacokinetics at doses ≥ 1 mg/kg. At

doses ≥ 1 mg/kg, the mean Cmax increased in a dose-proportional manner and was 26.0 µg/mL for the 1-mg/kg dose group and 486 µg/mL for the 20-mg/kg dose group. Similarly, at doses ≥ 1 mg/kg, the group mean AUC0-∞ had a range of 340−6050 day × µg/mL for 1-mg/kg and 20-mg/kg dose group and was approximately dose proportional, as evidenced by similar CL across the dose range. The observed CL and Vss for Atezolizumab at doses ≥ 1 mg/kg are consistent with these of a typical IgG1 antibody in humans. The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. Accordingly, the development of detectable ATAs does not appear to have a clinically significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. To date, no relationship between the development of measurable ATAs and safety or efficacy has been observed.

The expected metabolic products of proteins and peptides, including IgG1 monoclonal antibodies such as atezolizumab, are small peptides and individual amino acids. Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of Atezolizumab.

Contraindications

Atezolizumab is contraindicated for patients with the following:

- History of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins
- Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.

As with all investigational products, unknown side effects may occur. Patients should be monitored closely throughout their participation in clinical studies of Atezolizumab.

Availability

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

Atezolizumab will be delivered in infusion bags with IV infusion lines with product contacting surfaces of polyvinylchloride (PVC) and polyolefin and 0.2 µm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between v and PVC or polyolefin infusion materials (bags and infusion lines).

For further details, see the Atezolizumab Pharmacy Manual and IB.

Storage and handling

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. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Side Effects

Potential risks associated with Atezolizumab described here are based on observed nonclinical toxicities and adverse events observed in ongoing clinical trial(s) of Atezolizumab, as well as clinical toxicities related to monoclonal antibodies targeting the PD-L1/PD-1 pathway. Adverse events that have occurred within 24 hours after infusion include: infusion reactions, hypertension, fatigue, decreased appetite and headache.

Therapy with Atezolizumab may increase the risk of immune-related adverse events (IRAEs), including rash, hypothyroidism, hepatitis/transaminitis and colitis. Subjects should therefore be carefully monitored for evidence of clinically significant systemic IRAEs (e.g., SLE−like diseases) or organ-specific IRAEs (e.g., rash, colitis, uveitis, hepatitis, or thyroid disease).

Suggested workup for suspected IRAEs includes evaluation of the gastrointestinal tract, lung, liver, skin, eye, and pituitary and adrenal glands. Specific management of IRAEs is provided later in the protocol.

In addition, specific management for the toxicities occurring in the following organ systems is provided in this protocol: gastrointestinal tract (diarrhea, colitis), pulmonary (pneumonitis), hepato-biliary (hepatitis, pancreatitis), and dermatologic (rash, pruritus, severe cutaneous adverse reactions (SCARs)).

4.1.2 Tiragolumab

Classification

Tiragolumab is a fully human IgG1 monoclonal antibody. The recombinant antibody is produced in CHO cells, and consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each). There are two N-linked glycosylation sites (Asn306) in the Fc domain.

Mechanism of Action

Tiragolumab binds to TIGIT and prevents its interaction with Poliovirus receptor (PVR). The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes.

Pharmacokinetics and Metabolism

Preliminary population-PK analyses show that tiragolumab exposures increased approximately dose-proportionally following IV administration at doses ranging from 100 to 1200 mg Q3W as monotherapy or in combination with 1200 mg Q3W atezolizumab. Preliminary population-PK analysis estimated tiragolumab clearance at 0.28 L/day with a linear drug elimination half-life of approximately 15 days.

Contraindications

Tiragolumab is contraindicated for patients with a history of severe allergic anaphylactic reactions to chimeric, human, humanized antibodies, or fusion proteins because of the potential for severe reactions.

Availability

The tiragolumab drug product will be supplied in single-use, 15-mL glass vials. The vials contain 10 mL of tiragolumab drug product and are buffered in histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI. The approximate concentration of tiragolumab antibody in the vials is 60 mg/mL.

Storage and handling

The recommended storage condition for the tiragolumab drug product is 2°C-8°C (36°F–46°F). Do not shake or freeze IV bags containing dose solution. Protect from direct sunlight (exposure to indoor ambient light is acceptable).

Tiragolumab must be prepared for dosing under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The dose solution should be used immediately. If not used immediately, the total storage time of the dose solution prior to administration should not exceed 24 hours to limit the risk of microbial growth in case of accidental contamination.

Side Effects

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable. As an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated AEs [imAEs]). In addition, due to the intact Fc-effector function of tiragolumab, lymphopenia via ADCC is a theoretical risk. For information on the pharmacokinetics, metabolism, formulation and handling of tiragolumab, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

4.2 Accountability Records for Study Drug

The Investigational Pharmacist at each site will manage drug accountability records.

4.3 Ordering Study Drugs

UCSF will obtain Atezolizumab and Tiragolumab directly from Genentech as study supply. Drug will be shipped directly to subsites if required to ensure drug stability.

5 Treatment Plan

5.1 Dosage and Administration

Cohort A: The starting dose level of atezolizumab for Cohort A was 1200 mg administered by IV infusion on an outpatient basis for one dose, and was escalated in subsequent cohorts to 1200 mg administered by IV infusion every 3 weeks for a maximum of 3 neoadjuvant doses. Prior to Amendment 4.3 (October 19, 2020) subjects with adverse histology at the time of cystectomy (pT3, pT4, or N+) and no metastatic disease could elect to receive adjuvant MPDL3280A will receive 1200mg by IV infusion on an outpatient basis every 3 weeks for up to 16 doses cumulative doses.

Cohort B: The starting combination regimen will be atezolizumab 1200 mg administered by IV infusion on an outpatient basis every 3 weeks and tiragolumab 600 mg administered by IV infusion every 3 weeks for a total intended 3 neoadjuvant doses. As previously detailed, there will be a safety lead in of 6 initial patients at which time trial accrual will temporarily pause to assess the safety of combination treatment.

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

Atezolizumab and Tiragolumab will be delivered in infusion bags with IV infusion lines with product contacting surfaces of polyvinylchloride (PVC) and polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags and infusion lines).

The compatibility of tiragolumab with diluents other than described is unknown. Tiragolumab must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition. Infusions of blood products and any electrolyte supplementation must not occur simultaneously with infusion of tiragolumab.

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions (for subjects receiving more than 2 doses) may be delivered over 30 (± 10) minutes.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion, and during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

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 after consultation with the Study Chair.

Tiragolumab dose will be administered following the dose of atezolizumab and will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions (for subjects receiving more than 2 doses) may be delivered over 30 (± 10) minutes.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion, and during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of tiragolumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician after consultation with the Study Chair.

Table 5.1 Regimen Description

Study Drug	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Atezolizumab	None for 1st dose	1200mg	Intravenous	Day 1 each cycle	21 days
Tiragolumab (Cohort B only)	None for 1st dose	600mg	Intravenous	Day 1 each cycle	21 days

5.1.1 Other Modalities or Procedures

A radical cystectomy per institutional standard of care is planned for all patients enrolling in this study. No other procedures following initiation of systemic treatment (e.g., TURBT) are required for subjects while on study. Cystectomy may be performed beginning 3 weeks after the last planned dose of study therapy is administered. See study calendar (Section 6.10) for schedule of evaluations.

5.2 Cohort A Multi-dose Schedule

Three successive cohorts were enrolled to evaluate immunologic impact of escalating neoadjuvant doses of atezolizumab prior to cystectomy as outlined in the table below. A fixed dose of atezolizumab 1200mg was given with each cycle. For individual subjects there was no dose modifications above or reductions below the assigned dose allowed.

Table 5.2 Cohort A Multi-Dose Cohort Schedule

Dose Level	Dose of Atezolizumab	Number of Patients Accrued Before Accrual of Next Cohort
1	1200 mg x 1 dose	6
2	1200 mg q3 weeks x 2 doses	6
3	1200 mg q3 weeks x 3 doses	6

Multi-dose cohort accrual then proceeded according to the following: Dosing began in the first cohort (Dosing Level 1) with atezolizumab 1200mg IV x 1 dose. Beginning with this starting dose level, six patients were treated at each cumulative dose level. Accrual to the next higher

dose cohort began after 6 subjects in the lower cohort completed treatment and underwent cystectomy.

18 patients were treated in this multi-dose phase.

Cohort A Dose-expansion occurred at dose level 3 given no unacceptable treatment-related toxicity (as defined in Section 5.4) was observed. The rationale for expansion at this dose level is discussed in Section 1.8.

5.3 Cohort B Safety Lead-in Schedule

The Cohort B safety lead-in is described in section 3.1. Dosing for the Cohort B safety lead-in is detailed below. Once the intended treatment regimen is established following completion of the safety assessment, an additional 15 patients will be enrolled at the same regimen for a total of 21 patients on that treatment regimen.

Table 5.3 Cohort B Safety Lead-in Dosing

Dose Level	Atezolizumab	Tiragolumab
1	1200 mg q3 weeks x 3 doses	600mg x 3 doses
2	1200 mg q3 weeks x 3 doses	600mg x 2 doses
3	1200 mg q3 weeks x 3 doses	600mg x 1 dose

5.4 Dose Limiting Toxicities (DLTs)

Dose Limiting Toxicity (DLT) is an unacceptable treatment-related toxicity that occurs between time of first dose and time of cystectomy, defined as:

- any Grade 4 toxicity, or
- any recurrent Grade 3 toxicity, or
- any Grade 3 toxicity persisting more than 2 weeks, or
- any toxicity that results in delay of cystectomy beyond 12 weeks from the first dose of study drug

5.5 Interim Safety Analysis

A stopping rule for safety will halt accrual to the study and prompt reevaluation of the treatment regimen if unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 2 weeks), or treatment-related delay in cystectomy beyond 12 weeks (12 week window starts at time of first dose to time of cystectomy), is observed at a frequency of ≥ 33.3%.

Because of the known excellent safety profile of atezolizumab, this safety review will occur after all 6 subjects have been accrued to each individual dosing cohort in the Cohort A multi-dose phase and Cohort B safety lead-in and treated with at least one dose of study treatment, as well as on an ongoing basis should serious treatment-related toxicities or treatment-related delays in cystectomy be observed at any point in the study.

5.6 Dose Modifications and Dosing Delays

There will be no dose reduction for atezolizumab or tiragolumab for individual subjects in this study. Treatment delays are allowed for subjects who experience toxicity, as long as the following treatment occurs within the 12 week window between the first dose of study therapy and cystectomy. If any toxicity will delay cystectomy beyond 12 weeks from the time that patient begins study therapy, then no further study therapy should be given and the subject should proceed to cystectomy.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Study Chair approval. The acceptable length of interruption will depend on agreement between the investigator and the Study Chair and should conform with guidelines for delay of cystectomy above.

Treatment or visit delays for public holidays or weather conditions do not constitute a DLT or protocol violation.

5.7 Monitoring and Toxicity Management

5.7.1 Eligibility

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with atezolizumab and tiragolumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study- emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live-attenuated viral vaccine within 4 weeks before Day 1 are excluded from the study.

5.7.2 Monitoring

Each patient receiving atezolizumab, with or without tiragolumab, will be evaluable for safety. The safety parameters include but are not limited to all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients. Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events. For Cohort A, toxicity will be assessed according to CTCAE v4.0 and for Cohort B, toxicity will be assessed according to the CTCAE v5.0.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6-Study Schedule, Procedures and Observations. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see section 6 for the list and timing of study assessments). Laboratory values must be reviewed prior to each infusion.

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Section 7.5.2.7) will be reported in an expedited fashion. In addition, observed adverse events will be monitored on a regular basis.

Patients will be followed for safety for 30 days following their last dose of study treatment and for 2 years of follow up after cystectomy, or until they receive another anti-cancer therapy, whichever comes first.

Patients who have an ongoing study treatment-related adverse event 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 it has been determined that study treatment or participation is not the cause of the adverse event.

Interim Analyses for Safety are outlined in Section 5.5.

5.7.3 Management of General and Immune Related Adverse Events (irAEs)

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

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 or tiragolumab may not have an immediate therapeutic effect, and there is no available antidote for either drug. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, TNF-α inhibitors, or other immunosuppressants.

The primary approach to Grade 1-2 irAEs is supportive and symptomatic care; for higher grade irAEs, steroids by mouth or parenterally are given, and either delaying a dose or stopping therapy is appropriate. Recurrent Grade 2 irAEs may also mandate delaying a dose of atezolizumab and tiragolumab or the use of steroids. **If the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered off.** Consideration for benefit/risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab and tiragolumab. Atezolizumab and tiragolumab should be permanently discontinued in patients with life-threatening immune-related adverse events.

5.7.4 Management of Atezolizumab and Tiragolumab - Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab and tiragolumab 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.

Because of the expected pharmacologic activity of tiragolumab, the adverse event management guidelines described here, including those for continuing, withholding, resuming, and discontinuing atezolizumab, as outlined below, are applicable to tiragolumab as well as atezolizumab where noted.

Although most immune-related AEs 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 and/or tiragolumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute

management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab and/or tiragolumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab and/or tiragolumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.7.4.1 Pulmonary Events

Immune-mediated pulmonary events are a potential risk with tiragolumab.

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 the table below.

Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL= bronchoscopic alveolar lavage; IVIG= intravenous immunoglobulin

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Tiragolumab and 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before tiragolumab and 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 tiragolumab and atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.7.4.2 Hepatic Events

Immune-mediated hepatic events are a potential risk with tiragolumab.

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 the table below.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have 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.

Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	● Continue tiragolumab and atezolizumab. ● Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** ● Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** ● Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset. [a] ● Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. ● If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4	● Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c] ● Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. ● Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFTs = liver function tests.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Tiragolumab and 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

≤ 10 mg/day oral prednisone or equivalent before tiragolumab and 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 rechallenged with tiragolumab and atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.7.4.3 Gastrointestinal Events

Immune-mediated gastrointestinal events are a potential risk with tiragolumab.

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

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 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

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

Diarrhea or colitis, Grade 4	● Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor.[c] ● Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. ● Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. ● 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

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

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

5.7.4.4 Endocrine Events

Immune-related endocrine events are a potential risk with tiragolumab.

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 the table below.

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.

Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	● Continue tiragolumab and atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH weekly.
Symptomatic hypothyroidism	● Withhold tiragolumab and atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH weekly. ● Consider patient referral to endocrinologist. ● Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: ● Continue tiragolumab and atezolizumab. ● Monitor TSH every 4 weeks. TSH < 0.1 mU/L: ● Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	● Withhold tiragolumab and 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 tiragolumab and atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism.[c]
Symptomatic adrenal insufficiency, Grade 2−4	● Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to endocrinologist. ● Perform appropriate imaging. ● Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event resolves to Grade 1 or better 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 tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]
Hyperglycemia Grade 1 or 2	● Continue tiragolumab and atezolizumab. ● Initiate treatment with insulin if needed. ● Monitor for glucose control.

Hyperglycemia, Grade 3 or 4	• Withhold tiragolumab and atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume tiragolumab and atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2-3	• Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • Initiate hormone replacement therapy if clinically indicated. • If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor.[c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • Initiate hormone replacement therapy if clinically indicated.

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

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

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

5.7.4.5 Ocular Events

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

Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	● Continue tiragolumab and 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 tiragolumab and 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 tiragolumab and atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	● Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c] ● Refer patient to ophthalmologist. ● Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[A] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

[B] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to

≤ 10 mg/day oral prednisone or equivalent before tiragolumab and atezolizumab can be resumed.

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

5.7.4.6 Immune-Related Myocarditis

Immune-related myocarditis is a potential risk with tiragolumab and has been associated with the administration of atezolizumab.

Immune-related myocarditis should be suspected in any patient

presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g. in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

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

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

Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	● Refer patient to cardiologist ● Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	● Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. ● Refer patient to cardiologist ● Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. ● Consider treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement.[a] ● If event resolves to Grade 1 or better, resume tiragolumab and atezolizumab. [B] ● If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [C]

Immune-related myocarditis, Grade 3-4	● Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [C] ● Refer patient to cardiologist ● Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. ● Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. [A,b] ● 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.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

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

5.7.4.7 Infusion Related Reactions

No premedication is indicated for the administration of Cycle 1 of tiragolumab and atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 tiragolumab and atezolizumab may receive premedication with antihistamines, antipyretics, 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 tiragolumab and atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of tiragolumab and atezolizumab administration and are generally mild to moderate in severity.

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

Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of

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

IRR = infusion-related reaction.

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

5.7.4.8 Cytokine Release Syndrome

No premedication is indicated for the administration of Cycle 1 of tiragolumab or atezolizumab. However, patients who experience cytokine-release syndrome (CRS) with tiragolumab or atezolizumab may receive premedication with antihistamines, anti pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

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[29]. 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[30, 31], including atezolizumab.

Guidelines for medical management of CRS are provided below.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). 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.

Management Guidelines for 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 CRS.
Grade 2 [a] Fever [b] with at least one of the following: • Hypotension not requiring vasopressors • 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 as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue tiragolumab or atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of tiragolumab or atezolizumab may be administered. For subsequent infusions, consider

	administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Management Guidelines for Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with at least one of the following: • Hypotension requiring a vasopressor (with or without vasopressin) • Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue tiragolumab or atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.

Grade 4 [a] Fever [b] with at least one of the following: • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue tiragolumab or atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • 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).

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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 tiragolumab and atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. 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 consulting the Medical Monitor and considering the benefit-risk ratio.

f. Refer to Riegler et al.[32] for information on experimental treatments for CRS.

5.7.4.9 Pancreatic Events

Immune-related pancreatic events are a potential risk with tiragolumab.

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 work-up 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 the table below.

Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	● Continue tiragolumab and atezolizumab. ● Monitor amylase and lipase weekly. ● For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.

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

IV=intravenous

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

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

5.7.4.10 Dermatologic Events

Immune-related dermatologic events are a potential risk with tiragolumab.

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. 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 considered unless contraindicated. Management guidelines for dermatologic events are provided in the table below.

Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	● Continue tiragolumab and atezolizumab. ● Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	● Continue tiragolumab and atezolizumab. ● Consider patient referral to dermatologist. ● Initiate treatment with topical corticosteroids. ● Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	● Withhold tiragolumab and atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to dermatologist. ● Initiate treatment with 10 mg/day oral prednisone or equivalent, 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, resumetiragolumab and atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	● Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor.[c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: ● Withhold tiragolumab and atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.

Event	Management
	● 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, permanently discontinue tiragolumab and atezolizumab.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[A] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

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

5.7.4.11 Neurologic Disorders

Immune-related neurologic events are a potential risk with tiragolumab.

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 the table below.

Management Guidelines for Neurologic Disorders

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

IV=intravenous. Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Atezolizumab and tiragolumab 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. Protocol defined windows for treatment discontinuation may differ and should be followed accordingly.

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

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

5.7.4.12 Immune-Related Meningoencephalitis

Immune-mediated meningoencephalitis is a potential risk with tiragolumab.

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 the table below.

Management Guidelines for Immune-Related Meningoencephalitis

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

IV = intravenous. Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

5.7.4.13 Immune-Related Nephritis

Immune-related nephritis is a potential risk with tiragolumab has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non- steroidal anti- inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute

kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	● Continue tiragolumab and atezolizumab. ● Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	● Withhold tiragolumab and 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 tiragolumab and atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding tiragolumab and atezolizumab, permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	● Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. ● 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.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

[a] Atezolizumab and tiragolumab 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 Medical Monitor.

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

[c] Resumption of tiragolumab and 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 tiragolumab and atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

5.7.4.14 Immune-Related Myositis

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

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

Management Guidelines for Immune-Mediated Myositis

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

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

Note: Because of the expected pharmacologic activity of tiragolumab, guidelines for continuing, withholding, resuming, and discontinuing atezolizumab are also applicable to tiragolumab.

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

5.7.4.15 Hemophagocytic lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated 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 x 10^9/L (< 100,000/mL)
    - ANC < 1.0 × 10^9/L (< 1000/mL)
    - 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 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 x 10^9/L (≤ 181,000/mL)
- 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 below:

Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	· Permanently discontinue tiragolumab and atezolizumab and contact Medical Monitor. · Consider patient referral to hematologist. · Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. · Consider initiation of IV corticosteroids and/or an immunosuppressive agent and/or anti-cytokine therapy. · If event does not respond to treatment within 24 hours, contact Medical Monitor 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; MAS = macrophage activation syndrome.

5.8 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. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and tiragolumab but may be administered at the discretion of the treating physician after consultation with the Study Chair. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$ 2 at the discretion of the treating physician after consultation with the Study Chair.

The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, adrenocortical insufficiency, or for obstructive lung disease is allowed.

Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

Influenza vaccination should be given during influenza season only (approximately September to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study but may receive inactivated vaccine.

Patients who use hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer, 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 3.3 Eligibility Criteria) should continue their use.

Males and females of reproductive potential should use highly effective means of contraception.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

5.9 Excluded Therapy

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 5.8).
- Traditional herbal medicines should 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
- Patients who are receiving a receptor activator of nuclear factor kappa B ligand (RANK- ligand) inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study;

denosumab could potentially alter the activity and the safety of the study drugs.

- Initiation or increased dose of granulocyte colony-stimulating factors (e.g. granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is strongly discouraged.
- Patients are not allowed to receive immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, IL-2, or ipilumumab during the entire study. These agents, in combination with the study drugs, could potentially increase the risk for autoimmune conditions.
- Patients should also not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of the study drugs. Systemic corticosteroids and anti−TNF-α agents may attenuate potential beneficial immunologic effects of treatment with the study drugs but may be administered at the discretion of the treating physician after consultation with the Study Chair. If feasible, alternatives to these agents should be considered.
- In addition, all patients (including those who discontinue the study early) should not receive any other immunostimulatory agents for 10 weeks after the last dose of the study drugs.
- Patients who receive local therapy directed at the bladder (i.e., repeat TURBT, radiation therapy) after study treatment initiation but prior to cystectomy will be considered ineligible for response evaluation, but will remain eligible for safety and correlative evaluation. Such cases must be discussed with and approved by the Study Chair.

6 Study Schedule, Procedures and Observations

The study-specific assessments are detailed in this section. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed a window of ± 3 days unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

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.

The following apply to both screening assessments as well as to on study visits:

6.1 Informed Consent Forms and Screening Log

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records. Informed

Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

Each participating site is responsible for OnCore® registration of study participants consented at the site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

Demographic data will include age, ECOG performance status, sex, and self-reported race/ethnicity.

Cancer history will include an assessment of prior treatment with BCG.

6.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height (baseline only) and weight should be measured and recorded in the eCRF.

6.4 Vital Signs and Weight

Vital signs will include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressures while the patient is in a seated position, weight, oxygen saturation, and temperature. Patient height should be recorded once during the study either in the screening period or on cycle 1 day 1 prior to the first study treatment.

For the first infusion, the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Blood oxygen saturation will be measured at timepoints indicated in the study calendar using pulse oximetry.

6.5 Tumor Evaluation Methods

All subjects must have undergone cystoscopy or TURBT prior to study screening to document the presence of urothelial carcinoma.

Screening assessments must include CT scans of the chest, abdomen, and pelvis (with oral/IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis.

Screening bone imaging with either a technetium bone scan or a sodium-fluoride PET/CT is required only for subjects with an elevated alkaline phosphatase or symptoms to suggest bony metastasis. If bony metastases are detected at screening then the subject will be ineligible for study participation. Further bone-specific imaging should be performed as clinically indicated.

Imaging of the brain, head, and/or neck is not required for study entry but should also be performed if clinically indicated. If a CT scan for tumor assessment is performed using an FDG positron emission tomography (PET) /CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Results of standard of care tests or examinations performed prior to obtaining Informed Consent and ≤28 days prior to study entry may be used for the purposes of Screening rather than repeating such tests. Radiographic imaging assessments performed up to 45 days prior to study entry (i.e., available) may be used for the purposes of Screening.

For subsequent tumor assessments, procedures for tumor assessment should be performed as per the study calendar (see section 6.10) and clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). All known sites of disease (i.e., local lymph nodes) must be documented at screening and reassessed at each subsequent tumor evaluation. Relapse will be assessed by the investigator using RECIST v1.1 and modified RECIST criteria. The same evaluator should perform assessments if possible to ensure internal consistency across visits.

At the investigator's discretion, CT scans or bone-specific imaging should be repeated at any time if recurrent disease is suspected.

6.6 Laboratory, Biomarker, and Other Biological Samples

"Local" laboratory tests may be performed either at a local certified laboratory or at the study site. "Central" laboratory tests should be drawn at the study site and may be analyzed at the coordinating center or sent to Roche.

6.6.1 Local laboratory assessments

Local laboratory assessments may 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 including: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST,
- alkaline phosphatase, total protein, albumin and LDH
- C-reactive protein (CRP)
- Serum pregnancy test (only for women of childbearing potential, including premenopausal women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen)
- HBV DNA should be obtained prior to Cycle 1, Day 1 if patient has positive serology for anti-HBc Ab.
- HCV serology (anti-HCV antibody)
- HIV testing (if in accordance with national and/or institutional guidelines)
- The following laboratory tests will be performed **only** if there is clinical suspicion of acute immune-related toxicity. These should be performed at any point during the study if immune-related toxicity is suspected:
- Auto-antibody testing
- Anti-nuclear antibody (ANA)
- Anti−double-stranded DNA (Anti-dsDNA)
- Circulating anti-neutrophil cytoplasmic antibody (C-ANCA)
- Perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA)
- Epstein-Barr virus (EBV) serology
- Creatine kinase (CK) level

6.6.2 Central laboratory assessments

Central laboratories will coordinate the collection of archival tumor, fresh tumor, and leftover tumor tissue and blood samples for the assessment of atezolizumab and tiragolumab biomarkers, ATA assays, and auto-antibody testing. Instruction manuals and supply kits will be provided for all central laboratory assessments.

The following assessments will be performed at a central laboratory or Genentech:

- Anti-Therapeutic Antibody (ATA) assays and atezolizumab and tiragolumab levels (only in case of clinical suspicion of serious acute immune or inflammatory toxicity, related to atezolizumab and/or tiragolumab)
    - Serum samples will be assayed for the presence of ATAs to anti-atezolizumab and tiragolumab with use of validated

immunoassays. Atezolizumab and tiragolumab levels will be assessed using validated assays.

- T, B, and NK cell (TBNK) assays
- PD-L1 testing by IHC
    - Archival tissue blocks are slides will be shipped to a central lab for analysis of PD- L1 expression by IHC
- Biomarkers in tumor tissues
- RNA and DNA will be extracted from ~ 5 7μ sections for the analysis of genes associated with tumor immune biology as well as genomic mutations.
- Biomarker and immunologic assays in blood samples
    - Blood samples will be obtained for biomarker evaluation from all eligible patients at screening, before treatment, on treatment, at the treatment discontinuation visit, and in the follow-up period. Samples will be processed to obtain blood cells (and their derivatives), plasma, and serum for the determination of changes in surrogate biomarkers and immunologic assays that may be altered in UC or biomarkers that are related to UC and tumor immune biology (including but not limited to IFN-gamma and other exploratory biomarkers).
- Biomarker immunologic assays in urine samples
    - Urine samples will be obtained for biomarker evaluation from all eligible patients before study treatment, on treatment, and at the treatment discontinuation visit. Samples will be processed to obtain tumor cells (and their derivatives) and immune cells, for the determination of changes in surrogate biomarkers that may be altered in UC or biomarkers that are related to UC and tumor immune biology (including but not limited to IFN-gamma and other exploratory biomarkers).

Any remaining samples collected for biomarker assays, may be used for exploratory biomarker profiling and identification purposes as appropriate. In addition, exploratory biomarkers (including but not limited to markers related to immune or UBC biology) may be evaluated in tissue samples.

- Archival and fresh tumor tissue sample
    - Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, should be submitted prior to study enrollment.
    - Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, cell pellets, and lavage samples are not acceptable. For any core needle biopsy specimens, at least three cores should be submitted for evaluation.

  - Additional archival tumor specimens should be submitted if available.
  - Any fresh and/or paraffin embedded TURBT specimens (prior to study therapy or while on study therapy) or cystectomy specimens (after study therapy) will be made available for assessment of tumor response, and characterization of PD-1 and PD-L1 expression and of immunologic infiltrate.
  - For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are not eligible to enroll in the study will be returned no later than 4 weeks after eligibility determination.
- Tumor biopsy at the time of initial radiographic recurrence
  - All patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible as determined by the study investigator in consenting patients, at the first evidence of radiographic disease recurrence. Subjects may opt-out of this biopsy.
  - Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation. A fine needle aspirate is not acceptable.
- Use and storage of remaining samples from study-related procedures
  - The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations.

Please refer to the laboratory manual for additional details on laboratory assessments and sample handling.

6.7 Cardiac Tests: Electrocardiograms (ECGs)

Twelve-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

6.8 Anti-Therapeutic Antibody and atezolizumab and tiragolumab Testing

Atezolizumab and/or tiragolumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab and/or tiragolumab will be closely monitored.

Validated assays will be employed to detect ATAs and atezolizumab and/or tiragolumab levels if warranted based on clinical suspicion of ATA development.

6.9 Study Schedule

6.9.1 Screening

The Screening procedures and assessments must be completed **within 28 days** of the Day 1 Visit. Local and Central laboratory assessments done within 14 days of beginning treatment do not need to be repeated for Cycle 1 Day 1.

- Physical examination
- Vital signs
- Complete medical history
- Baseline conditions assessment
- Documentation of disease
- Performance status
- History of prior treatments and any residual toxicity relating to prior treatment
- Baseline medications taken within 7 days of Day 1
- Archival sample of tumor tissue acquisition. Acquisition of representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing for tumor PD-L1 expression and immune characterization.
- Laboratory assessments:
    - Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
    - Serum chemistries including: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH
    - C-reactive protein (CRP)
    - Serum pregnancy test (only for women of childbearing potential, including premenopausal women who have had a tubal ligation) **must be performed within 14 days of cycle 1 day 1.**
    - Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
    - Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
    - HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen)

- HBV DNA should be obtained prior to Cycle 1, Day 1 if patient has positive serology for anti-HBc Ab.
- HCV serology (anti-HCV antibody)
- HIV testing (if in accordance with national and/or institutional guidelines)
- Serum will be banked and frozen during screening for the following assays in all patients, however these assays will only be run to establish baseline values *if there is clinical suspicion of acute immune-related toxicity related to* atezolizumab and/or tiragolumab:
  - Auto-antibody testing, including ANA, Anti-dsDNA, C-ANCA, P-ANCA
- EBV serology (See Section 3.3.2 Exclusion Criteria)
- Creatine kinase (CK) level

- Central laboratory assessments
  - TBNK blood sample
  - Urine sample for cytokine assessment.
- Imaging (CT or MRI) of the chest, abdomen, and pelvis for tumor/lesion assessment. These assessments may be performed up to **45 days** prior to study entry. Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram should be performed if clinically indicated.
- Electrocardiogram (ECG)
- Bone scan (technetium OR sodium-fluoride PET/CT) (only for subjects with an elevated alkaline phosphatase or clinical suspicion of bony metastatic disease)

6.9.2 Treatment Period

Day 1 of all cycles (+/- 3 days for cycles ≥2)

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Local laboratory assessments. Unless otherwise noted, they may be obtained up to 96 hours prior to day 1 of each cycle:
  - CBC with differential and platelet count

  - Blood chemistry assessment, including: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT,
  - AST, alkaline phosphatase, total protein, albumin and LDH
  - C-reactive protein
  - Urinalysis
- Central laboratory assessments
  - Immunologic and pharmacodynamic evaluations
  - TBNK blood sample
  - Plasma, serum, and blood sample for PD biomarkers
  - Urine sample for cytokine assessment.
- Atezolizumab/tiragolumab infusion. See section 5.1 for dosing and administration requirement.

6.9.3 End of Treatment (prior to cystectomy)

To be completed within 30 days of the last dose of study drug and prior to cystectomy.

- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications
- Local Laboratory Assessments. Unless otherwise noted, they may be obtained up to 96 hours prior to the visit:
  - Hematology assessment, including CBC with differential and platelet count
  - Blood chemistry assessment, including: glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin
  - C-reactive protein
  - Urinalysis
  - TSH, T3 and T4
- Central laboratory assessments
  - Immunologic and pharmacodynamic evaluations
  - TBNK blood sample
  - Plasma, serum, and blood sample for PD biomarkers
  - Urine sample for cytokine assessment.
- Imaging (CT or MRI) of the abdomen, and pelvis for tumor/lesion assessment, and if clinically indicated, imaging of the chest (CXR or CT).

Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram should be performed if clinically indicated.

- No repeat TURBT is required after the initiation of study therapy, however if performed per institutional standard of care then any tissue or other tumor biopsy should be obtained for analysis.

6.9.4 Post-cystectomy/Follow Up Visits

Patients will be followed every 4 weeks (+/- 1 weeks) from the time of cystectomy for 12 weeks, and thereafter every 12 weeks for up to 2 years after cystectomy or until disease progression, death, study termination, or withdrawal from study, whichever occurs first.

- Radiographic imaging should occur every 12 weeks and at end of treatment as outlined in the study calendar.
- The following Central Laboratory tests should be obtained every 12 weeks
    - TBNK blood sample
    - Plasma, serum, and blood sample for PD biomarkers
    - Urine sample for cytokine assessment.

Once all therapy is completed patients should be followed every 12 weeks until the completion of 2 years after cystectomy or until disease progression, death, study termination, or withdrawal from study, whichever occurs first.

Patients who discontinue study treatment prior to cystectomy for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments until the patient dies, experiences disease progression, withdraws consent, for 2 years from the last dose of study therapy or until the study closes, whichever occurs first.

Patients who start a new anti-cancer therapy (i.e. adjuvant chemotherapy) in the absence of disease progression should continue to be followed for progression according to the protocol schedule of response assessments unless they withdraw consent, experience disease progression, death, study termination, or withdrawal from study, whichever occurs first.

In addition to tests performed per local standard of care, the following procedures will be performed at the Follow Up Visit(s):

- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
    - After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug.
- Concomitant medications

- Pathologic review of tumor response (first follow up visit only)
- Local Laboratory Assessments. Unless otherwise noted, they may be obtained up to 96 hours prior to the visit:
    - Hematology assessment, including CBC with differential and platelet count
    - Blood chemistry assessment, including: glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin,
    - ALT, AST, alkaline phosphatase, LDH, total protein, and albumin
    - C-reactive protein
    - Urinalysis including urine cytology
    - TSH, T3 and T4
- Central laboratory assessments
    - Immunologic and pharmacodynamic evaluations
    - TBNK blood sample
    - Plasma, serum, and blood sample for PD biomarkers
    - Acquisition of cystectomy tissue (either fresh or paraffin embedded) for immunologic characterization.
- Imaging
    - CT or MRI of the abdomen and pelvis for tumor recurrence to be performed every 12 weeks.
    - Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram should be performed per institutional standard of care.
    - Chest imaging (Chest X-ray or CT Chest) every 12 weeks.
- Tumor tissue (only at the first evidence of radiographic disease recurrence)
    - Mandatory tumor biopsy sample collection, if clinically feasible as determined by the study investigator in consenting patients. Subjects may opt-out of this biopsy.
    - Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation. A fine needle aspirate is not acceptable.

6.9.5 End of Study Visit

In addition to tests performed per local standard of care, at 1 month (allowed up to 2 months) off study the following procedures will be performed at the End of Study Visit:

- Physical examination

- Vital signs
- Performance Status
- Evaluation of adverse events
    - After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug.
- Concomitant medications
- Pathologic review of tumor response (if not already performed)
- Local Laboratory Assessments. Unless otherwise noted, they may be obtained up to 96 hours prior to the visit:
    - Hematology assessment, including CBC with differential and platelet count
    - Blood chemistry assessment, including: glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin,
    - ALT, AST, alkaline phosphatase, LDH, total protein, and albumin
    - C-reactive protein
    - Urinalysis including urine cytology
- Central laboratory assessments
    - Immunologic and pharmacodynamic evaluations
    - TBNK blood sample
    - Plasma, serum, and blood sample for PD biomarkers
    - Acquisition of cystectomy tissue (either fresh or paraffin embedded) for immunologic characterization (if not done already performed)
- Imaging (only required if not performed within the last 8 weeks)
    - CT or MRI of the abdomen and pelvis
    - Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram should be performed per institutional standard of care.
    - Chest imaging (Chest X-ray or CT Chest)
- Tumor tissue (only at the first evidence of radiographic disease recurrence, if not already performed)
    - Mandatory tumor biopsy sample collection, if clinically feasible as determined by the study investigator in consenting patients. Subjects may opt-out of this biopsy.
    - Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps

biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation. A fine needle aspirate is not acceptable.

6.9.6 Long Term/Survival Follow-up Procedures

Following early discontinuation all patients will be followed for 2 year relapse free survival and subsequent anti-cancer therapy. Survival and subsequent anti-cancer therapy follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, for up to 2 years after cystectomy. Subjects will not be followed for overall survival.

6.9.7 Discontinuation of Therapy

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 or adverse event that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance
- Any significant uncertainty on the part of the Investigator that continued participation is prudent.

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 eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

Patients who withdraw from the study *after a dose of study therapy has been administered* will not be replaced.

6.9.8 Study Treatment Discontinuation

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

- Symptomatic deterioration (i.e., uncontrollable pain secondary to disease) attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab and/or tiragolumab, including development of an immune-related adverse event (irAE) determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment

- Use of another non-protocol anti-cancer therapy (see Section 5.9)
- Pregnancy
- The primary reason for study treatment discontinuation must be documented in the eCRF.

6.10 Study Calendar

	Screening[a]	All Cycles	Treatment Discontinuation[b]	Post-cystectomy	Follow-Up	Off Study
Assessment Window (Days)	**Day -28 to Day -1**	**Day 1 (± 3 Days for Cycles ≥ 2)**	**≤ 30 Days after Last Dose, prior to cystectomy**	**Every 4 weeks (+/- 1 week) x 12 weeks total[z]**	**Every 12 weeks (+/- 2 weeks)**	
Informed Consent	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information	x					
Concomitant medication[c]	x	x	x	x	x	x
Adverse events[d]	x	x	x	x	x	x
Tumor tissue acquisition or 15 unstained slides [e]	x			x[k]	x[k]	
Treatment administration						
Atezolizumab infusion[f] (Cohort A)		x				
Atezolizumab and Tiragolumab infusion[f,g] (Cohort B)		X				
Clinical procedures						
Complete physical examination[h]	x	x	x	x	x	x
Performance status[h]	x	x	x	x	x	x
Vital signs[i]	x	x	x	x	x	x
Oxygen saturation (pulse oximetry)	x	x	x	x	x	x
Tumor assessments[j]	x			x	x	x
Survival and anti-cancer therapy follow-up [l]					x	x
Laboratory procedures[h]						
Hematology[m]	x	x	x	x	x	x
Serum chemistry[n]	x	x	x	x	x	x
Urinalysis[o]	x	x	x	x	x	x
Urine sample	x	x	x	x	x	x

	Screening[a]	All Cycles	Treatment Discontinuation[b]	Post-cystectomy	Follow-Up	Off Study
Assessment Window (Days)	**Day -28 to Day -1**	**Day 1 (± 3 Days for Cycles ≥ 2)**	**≤ 30 Days after Last Dose, prior to cystectomy**	**Every 4 weeks (+/- 1 week) x 12 weeks total[z]**	**Every 12 weeks (+/- 2 weeks)**	
Pregnancy test (HCG)[p]	X					
TSH, free T3, free T4	X		X			
HIV, HBV, and HCV Serology[q]	X					
CRP	X	X	X	X	X	X
Serum banking for baseline auto-antibody testing[r]	X					
EBV serology[s]	X					
CK[t]	X					
TBNK blood sample[u]	X	X	X	X	X	X
Plasma, serum, and blood sample for PD biomarkers[u]		X	X	X	X	X
Imaging procedures						
ECG[v]	X					
Chest imaging[w]	X			X [x]	X	X
Bone scan[x]	X					
Abdominal imaging (CT or MRI)	X		X	X [x]	X	X

anti-HBc = hepatitis B core antigen; ATA = anti-therapeutic antibody; EBV = Epstein-Barr virus; HBV = hepatitis B virus, HCV = hepatitis C virus; MRI = magnetic resonance imaging; TBNK = T, B, and NK cells; TSH = thyroid-stimulating hormone; CK = creatine kinase.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

a. Examinations performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests, and within 45 days for radiographic imaging. If patients are declining cisplatin-based chemotherapy the reason must be documented.
b. All patients will return within 30 days for a follow up visit, including those who discontinue study therapy early.
c. See Section 5.8.
d. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

e. Only tumor tissue from initial TURBT and cystectomy are required per protocol. Tumor tissue from TURBT should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, and cytologic cell pellets are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Ideally, a tumor specimen obtained after completion of the most recent therapy should be submitted. Any archival tumor specimen, if available, should also be submitted. **Repeat TURBT or other tumor biopsies are not required after the start of therapy, prior to cystectomy, however if done at any point per local standard of care then all tissue available should be acquired.**
f. For both atezolizumab and tiragolumab, the initial dose of study drug will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, 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.
g. Tiragolumab dose will be administered following the dose of atezolizumab. If one agent (either atezolizumab or tiragolumab is held then both study drugs should be held.
h. ECOG performance status, physical examination, and local laboratory assessments (CBC, serum chemistries, urinalysis) may be obtained ≤ 96 hours before the scheduled visit. Laboratory procedures measured within 14 days of beginning treatment do not need to be repeated on Cycle 1 Day 1.
i. Vital signs include heart rate, respiratory rate, blood pressures, temperature, weight, and oxygen saturation. Height should be recorded once during screening or prior to cycle 1 day 1. For first infusion of study treatment, the patient's vital signs should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.
j. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure should be used throughout the study for each patient. Available results must be reviewed by the investigator before dosing at the next cycle. Pathologic review of tumor response should occur at the first follow up visit after cystectomy. Patients will undergo assessments for tumor recurrence every 12 weeks (+/- 2 weeks) for the first 2 years following cystectomy. Patients who discontinue from the initial treatment stage for reasons other than disease progression (e.g. toxicity) will continue scheduled tumor assessments until disease recurrence, withdrawal of consent, or death. Patients who start a new anti-cancer therapy in the absence of disease recurrence (e.g. adjuvant therapy) should be followed according to the protocol schedule unless they withdraw consent. Investigators may perform additional scans or more frequent assessments if clinically indicated.
k. Tumor biopsy at recurrence, preferably at the time of radiographic progression. Patients may opt out of this biopsy. Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation.
l. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor. All patients will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.
m. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated.
n. Serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin and LDH
o. Specific gravity, pH, glucose, protein, ketones, and hemoglobin.
p. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1.
q. HIV testing to be performed in accordance with national and/or institutional guidelines. Hepatitis B surface antigen, anti-HBc antibody and anti-HBs antibody should be collected during screening. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be collected prior to Cycle 1, Day 1.
r. Serum will be banked and frozen during screening, however these assays will only be run to establish baseline values *if, at a later point in the study, there is clinical suspicion of acute immune-related toxicity related to* study drug.
s. Perform Epstein-Barr virus (EBV) viral capsid antigen IgM test at screening (See Section 3.3.2 Exclusion Criteria)
t. Perform creatine kinase (CK) testing at screening, and as clinically indicated as determined by the Investigator
u. See Appendix 4 for details
v. ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting and in a supine position prior to ECG collection.

w. Chest CT is required for screening. Chest X-ray or Chest CT are acceptable in the follow-up phase for surveillance for tumor recurrence, per institutional guidelines. If clinical suspicion of recurrent disease in the chest a CT scan should be performed.
x. Bone scan (Technetium or Sodium-fluoride PET/CT required at screening only for subjects with an elevated alkaline phosphatase or clinical suspicion of bony metastatic disease. Further imaging for subjects on study only as clinical indicated.
y. Chest and abdominal imaging at the 12 week post cystectomy visit, does not need to be done earlier unless clinically warranted

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy

7.1.1 Pathologic Response

Treatment efficacy will be determined by the pathologic determination of tumor response at the time of cystectomy. This will include determination of tumor response in the bladder as well as in any resected lymph nodes.

Pathologic determination should be in accord with collaborative guidelines[33] and should specifically proceed as follows:

For all cystectomy specimens the pathologist will cut the tissue at roughly 0.5cm intervals to look for a tumor mass. If no tumor mass is seen on gross examination then representative sections should be put in. If cystoscopic abnormalities are noted by the treating Urologist, then the treating Urologist will indicate location of cystoscopic abnormalities (up to 4 different ones) on the pathology requisition, and that pathologists will "block in" each of these areas (up to 4 different areas) during pathologic evaluation of the bladder to cover at least 1 cm square area of each indicated location. This is in addition to any grossly-recognized residual tumor foci that are seen when opening the bladder for pathologic evaluation.

It is similarly recommended that prior surgical sites or mucosal ulcerations be sampled in their entirety for residual tumor and adequate mapping performed. Furthermore, areas that appear red and regions of mucosal induration should be sampled to rule out CIS. There is no need for complete embedding of the entire bladder wall. Communication between the urologic surgeon and pathologist is key in cases where prior surgical sites, mucosal ulcerations, or alterations are not evident to ensure that appropriate tissue sampling occurs.

The following definitions apply to determination of pathologic responses:

Evaluable for pathologic complete response

Only those patients who have received at least one cycle of therapy, and have had their disease evaluated pathologically at the time of resection will be considered evaluable for pathologic response. These patients will have their response classified according to the pathologic complete response definitions below:

- **Pathologic complete response (pCR):** Defined as the presence of pT0 disease. Similarly there must be no evidence of tumor in all resected lymph nodes (N0).
- **Near pathologic complete response (near pCR):** Defined as the presence of Ta or Tis disease (or both) in the resection specimen, without evidence of any higher stage disease elsewhere or evidence of tumor in all resected lymph nodes (N0).

All patients will be followed for 2 years post-cystectomy to evaluate for tumor recurrence.

7.1.2 Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI

92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

7.1.2.1 Definitions

Evaluable for toxicity

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

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated prior to resection will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

7.1.2.2 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measurable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable. (e.g. PSA, CA-125, CA19-9, CEA)

7.1.2.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment (for example CT or MRI) and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

7.1.2.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes).

There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

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

Table 7.1 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression				

Duration of Response

Duration of overall response

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

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

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

Disease-Free Survival

Disease-free survival (DFS) is defined as the duration of time from start of treatment to time of documented disease recurrence.

7.2 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use CTCAE v4.0 for Cohort A and will use CTCAE v5.0 for Cohort B for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, see section 5.7.

7.2.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to study drug, all events of death, and any study specific issue of concern.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

7.2.2 Definitions of Adverse Events

7.2.2.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

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 transitional cell carcinoma of the bladder that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

7.2.2.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.2.2.3 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

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

Yes (definite, probably, possible, unlikely)

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

No (unrelated)

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

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

7.2.2.4 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.2.2.5 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- Significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.3 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 FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

7.4 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 any study procedures and ends 30 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.

7.5 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.5.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints 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?"

7.5.2 Specific Instructions for Recording Adverse Events

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

7.5.2.1 Diagnosis vs. Signs and Symptoms

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

7.5.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 7.3.3), 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".

7.5.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be

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

7.5.2.4 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 subject 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 subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

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

7.5.2.5 Pregnancy

If a female subject or a female partner of a male subject becomes pregnant while receiving investigational therapy or within 5 months of the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. 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 and/or tiragolumab should be reported as an SAE.

7.5.2.6 Post-Study Adverse Events

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

7.5.2.7 Adverse Events of Special Interest (AESIs)

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

Adverse events 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 elevated bilirubin or clinical jaundice, as defined by Hy's Law
  - o Treatment-emergent ALT or AST 3 ULN in combination with total bilirubin 2 ULN
  - o Treatment-emergent ALT or AST 3 ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, defined as: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal

product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: Diabetes mellitus, Pancreatitis, or Adrenal Insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>$ 10 $\times$ upper limit of normal
- Systemic Lupus Erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, cytokine release, influenza like illness, SIRS, or infusion reaction syndromes, hemophagocytic lymphohistiocytosis (HLH), and macrophage activating syndrome (MAS)
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, and optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, or toxic epidermal necrolysis)

7.5.2.8 Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

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 complaints
  - 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.

7.5.2.9 Recording of an Adverse Event

Adverse Events will be recorded as described in the Data Safety Monitoring Plan (Appendix 2)

7.6 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.7 Reporting Requirements for Pregnancies

7.7.1 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 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted to Genentech. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The Sponsor-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. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided in Section 7.9.4).

7.7.2 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 5 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. 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. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF 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.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 7.7.1.

7.7.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to Genentech immediately (i.e., no more than 24 hours after learning of the event; see above). Abortion, whether accidental, therapeutic, or spontaneous should be reported in the same fashion (because Genentech considers spontaneous abortions to be medically significant events).

7.8 Adverse Events Monitoring

Refer to the Data Safety Monitoring Plan, located in Appendix 2

7.9 Expedited Reporting

7.9.1 Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

7.9.2 Reporting to UCSF Institutional Review Board

The UCSF PI must report events to the UCSF IRB according to institutional guidelines.

UCSF IRB website for guidance in reporting adverse events: https://irb.ucsf.edu/adverse-event

The PI at each participating site is responsible for reporting events to the IRB of record according to IRB guidelines.

The sponsor (UCSF) will be responsible for the distribution of safety information to participating investigators, where relevant, in accordance with local regulations.

7.9.3 Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

7.9.4 Expedited Reporting to Genentech

Investigators will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in female partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to Genentech Product. The completed Medwatch report should be sent via fax or email to Genentech Drug Safety at:

Fax: [redacted]

Email: [redacted]

And all Product Complaints without an AE should be reported via:

PC Hotline Number: [redacted] (M-F: 5 am to 5 pm PST)

Investigators must report all the above mentioned single case reports adequately to Genentech on a MedWatch form within one (1) business day of the awareness date

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report Genentech.

7.9.5 Case Transmission Verification of Single Case Reports

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

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

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

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

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

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

Tel: [redacted]

Fax: [redacted] or [redacted]

7.9.6 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

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

7.9.7 Follow-up Information

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

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

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

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

7.9.8 7.9.8 Aggregate Reports

IND Annual Reports: All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be emailed to Genentech Drug Safety:

Genentech Drug Safety CTV mail box: [redacted]

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

7.9.9 7.9.9 Study Close-Out

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

[redacted]

And to Genentech Drug Safety CTV oversight mail box at: [redacted]

7.9.10 7.9.10 Queries

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

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

7.9.11 7.9.11 Safety Crisis Management

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

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

7.9.12 7.9.12 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.

8 Statistical Considerations and Evaluation of Results

8.1 Determination of Sample Size and Power Calculation

Cohort A

Multi-dose phase: With 6 patients in each cohort, there will be 80% of power to detect the effect size of 1.5 at significance level of 0.1. For the lowest dose level, a 2-fold increase from pre-treatment to post- treatment is expected, if at the higher dose level, there is more than 3-fold increase, assuming the standard deviation equals 1, then there will be 80% power to detect significant treatment effect on the intratumoral immune response.

Expansion phase: Data from a study of intravesical valrubicin chemotherapy in BCG refractory patients[34] demonstrated that a 21% CR rate is achievable at 6 months. Assuming a 5% (null) CR rate for untreated patients at 6 months, 15 patients would be required to observe an improvement to a 36% CR rate at 6 months in response to-PD-L1 therapy (effect size = 0.642), at a significance level of 0.1 with 80% power.

Cohort B

A pT0 rate at cystectomy was observed for ~30% of patients treated with immune checkpoint inhibitors monotherapy based on published Phase II clinical trials. In order to observe an improvement from a 30% CR rate (null hypothesis) to 60% CR rate (alternative hypothesis) with the combination of atezolizumab and tiragolumab a total of 21 patients are required in Cohort B assuming a significance level of 0.05 and 80% power.

Using these assumptions, following a lead in safety phase of 6 patients at a combination regimen that is deemed to be safe based on the criteria outlined above, a further 15 patients will be enrolled at the same regimen. This will make a total of 21 patients to be treated in Cohort B with the intended regimen.

8.2 Interim Analyses and Stopping Rules

A stopping rule for safety will halt accrual to the study and prompt reevaluation of the regimen if unacceptable treatment-related toxicity (defined as any Grade 4 toxicity, any recurrent Grade 3 toxicity, or any Grade 3 toxicity persisting more than 2 weeks), or treatment-related delay in cystectomy beyond 12 weeks (including both the treatment period and any delay due to an adverse event), is observed at a frequency of ≥33.3%

No formal interim stopping rule for efficacy will be performed. This is due to the fact that immune therapies may require weeks to months to have efficacy, and therefore the true antitumor activity of atezolizumab and tiragolumab may not be apparent at the time of cystectomy. Rather, durable immune responses may be generated against the tumor and may prevent post-cystectomy recurrence; this effect may not be detectable for months to years after study drug administration.

Furthermore, given the relatively small sample size of this study an interim stopping rule for futility based on longer-term clinical endpoints (i.e. relapse-free survival) is not considered feasible or warranted.

8.3 Analysis Plans

8.3.1 Analysis Population

All patients who receive any part of a dose of any study drug will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any dose of study therapy may be replaced after discussion with the Study Chair. Subjects who have received any dose of study therapy will not be replaced.

Demographic and baseline characteristics will be summarized. In general, frequency distribution and percentage will be used to summarize categorical measurements, while mean with standard deviation and median with range will be used to describe symmetric and skewed continuous measurements, respectively. Univariate analysis among variables will be assessed using the two-sample t-test, Wilcoxon-rank-sum test, Chi- square test, as appropriate.

8.3.2 Analysis of Primary Endpoints

The immunologic effect of activity study therapy within bladder tissue will be measured by a change in the $CD3^+$ T cell count/μm^2 between the pretreatment biopsy and the cystectomy tissue following study therapy administrations. Immunohistochemistry will be performed in the Fong lab at UCSF per established SOPs. Based on prior experience tissue will be designated into 3 distinct compartments: benign epithelium, tumor centers, and tumor interfaces. Tumor interfaces will be defined as fields where malignant and benign epithelium are present. Automatic cell counts for single- and double-stained cells will be determined for each field with color-specific algorithms.

The cell count for each compartment will be reported as the mean for each of the five quantitated fields. Cells of interest will include CD3+ T cells, CD3+ Ki67+ proliferative T cells,

CD4+ FoxP3- helper T cells, CD4+ FoxP3+ regulatory T cells, CD8+ cytotoxic T cells, as well as PD-1 expression on the different lymphocytes. In collaboration with Genentech, PD-L1 expression on both tumor and immune cells within the microenvironment will be assessed.

For each cohort, the change of T cell counts from pre-treatment to post-treatment will be calculated for each compartment as log2 of the ratio of post-treatment vs. pre-treatment counts. If different regimens are used (for example atezolizumab x 3 doses and tiragolumab x 2 doses) two-sample Wilcoxon rank sum test will be used to compare the difference of the change from pretreatment to post-treatment between cohorts to assess if the intratumoral immune response associated with increasing numbers of treatments. No multiple comparison adjustments will be performed.

8.3.2.1 pT0 rate

Point estimates and 95% confidence intervals of pathologic T0 rate at the time of cystectomy as defined in Section 7.1.1 will be obtained for subjects treated with atezolizumab and tiragolumab. Pathologic T0 rate at the time of cystectomy will be compared with the null hypothesis rate (see Section 8.1) separately by using one-sample proportion test.

8.3.2.2 Safety

Adverse events occurring prior to surgery will be summarized by maximum toxicity grade for all patients treated with the particular regimen. The toxicity grade for laboratory data will be calculated using NCI CTCAE-v4.0 for the (already accrued) Cohort A and using CTCAE-v5.0 for Cohort B, and the lab data will be summarized according to the subjects' baseline grade and maximum grade for each cycle of therapy. The percentage of subjects requiring a treatment-related delay in surgery beyond 12 weeks from study start will be summarized using descriptive statistics. All treatment related adverse events that lead to delay in cystectomy will be graded using NCI CTAE-v4.0 or 5.0 as discussed above and will be recorded.

8.3.3 Analysis of Secondary Endpoints

8.3.3.1 Near complete pathologic response rate, 2 year relapse-free survival, 2 year overall survival

Point estimates and 95% confidence intervals of the near complete pathologic response rate, defined as the presence of only pTa or pTis in patients with T2 of greater disease at baseline, the 2 year RFS rate defined from study start until recurrence of disease or death from any cause, and the 2 year overall survival (OS) rate defined from study start until death from any cause, will be obtained for patients enrolled in the study, and compared with the null hypothesis rate (see Section 8.1) separately by using one-sample proportion test. RFS and OS will be obtained by Kaplan Meier method for the ITT population.

8.3.3.2 PD-1/PD-L1 expression and response

For each dose level as well as for each individual expansion cohort, Fisher's exact test will be used to test the association of baseline tumor and T-cell PD-L1/PD-1 immunohistochemical expression with disease response.

8.3.4 Analysis of Exploratory Endpoints: Tissue based endpoints

Note: Tissue will be used for multiple different exploratory assays. In the event that there is insufficient tissue to perform all assays for an individual subject, the tissue should be prioritized

for assays as follows, in which the first assay described is the highest priority. Also note that PD-L1 immunohistochemistry and immune cell mRNA signature assays will be performed at Genentech, while all other assays will be performed at UCSF.

8.3.4.1 Tumor PD-L1 assessment

PD-L1 protein expression on tumor tissue from pre-treatment biopsies, cystectomy specimens, and any other tumor biospecimens obtained will be evaluated immunohistochemically and scored on a scale of 0, 1, 2, or 3. This scoring will be used for the determination of relationships between tumor PD-L1 expression and clinical responses described above.

8.3.4.2 Tissue immune subset quantification and localization

For all subjects, immune cell subsets and localization will be summarized by changes from baseline to after treatment using descriptive statistics.

8.3.4.3 Immune cell mRNA signatures of response

To identify individual genes whose expression levels at pre-treatment are associated with pCR, we will apply two-sample *t* tests to compare responders and non-responders. Adjusted P values controlling for false discovery rate (Benjamini and Hochberg method) will be derived. In addition, to assess association of pre-specified immune gene signature with response, the median expression level of the component genes will be used to represent the signature and two-sample t tests will be used. For genes or signatures that emerge as significantly associated with response, logistic regression models will be used to assess their independent association with response after adjusting for known clinical prognostic factors. To identify pharmacodynamic markers, paired t-test will be carried out to examine immune gene expression differences between pre-treatment and at-cystectomy samples. Additionally, association of gene expression levels at time of cystectomy with long term efficacy outcomes, such as PFS and DFS, will be explored using the Cox proportional hazards regression model. Hierarchical clustering superimposed with response status, relevant baseline or prognostic characteristics or experimental factors will be performed using Spearman correlation and complete linkage to visualize the discriminating power of the immune gene expression and the correlative structure among the genes and the samples.

8.3.4.4 T cell receptor (TCR) deep sequencing

For each individual dose level, and for each dose-expansion cohort the change in tumor-infiltrating TCR between pre-treatment and post-cystectomy after treatment will be assessed by calculating the number of unique clonotypes comprising the top 25^{th} percentile of cumulative reads after sorting by clone abundance. Repertoire change between sequencing experiments will be measured using Morisita's distance.

8.3.4.5 Genomic signatures of response

It is hypothesized that tumors with highly mutated or copy-aberrant genomes will either overexpress native proteins or express novel mutant proteins, both of which may be recognized by the immune system and serve as tumor-specific antigens. Therefore the effect of genomic mutations on the immune landscape will be investigated in each of the expansion cohorts in this study as follows.

Tumor DNA will be isolated from pre-treatment tissue and from post-cystectomy specimens, and will be analyzed for copy number using the Human Genome CGH 244K Microarray (Agilent, Santa Clara, CA) and/or by next-generation sequencing. Results will be analyzed with DNA Analytics software (Agilent) and with the assistance of the UCSF Genome Core and the UCSF Biostatistics core. For copy number paired Wilcoxon signed-rank test will be applied to test difference of tumor gene copy number between pre and post treatment. Two-sample Wilcoxon signed-rank test will be used to test the gene copy number between tumor responders and non-responders for pre-treatment, post-treatment and changes before and after the treatment, separately. Multiple testing adjustment will be done by controlling false positive rate. Next-generation sequencing will take place using appropriate methods and biostatistical analyses.

Annotation will be based on NCBI and UCSC databases. Chi-square test will be applied to obtain the significant variants associated with the clinical response.

8.3.5 Analysis of Exploratory Endpoints: Immune endpoints

8.3.5.1 Immune cell activation

For each cohort individually, and for each individual expansion cohort, flow cytometry of circulating immune cell subsets will also be performed on pre-treatment blood and again after cystectomy. Established flow cytometry panels will examine T cell activation. Immune cell quantification will be summarized by changes from baseline to after treatment using descriptive statistics. Furthermore, paired Wilcox on signed-rank test will be applied to test the pre-post treatment changes. When available, immune cells digested from resected tumor tissues will also be assessed by flow cytometry.

8.3.5.2 Circulating antibody detection and characterization

Spotted antigen arrays will be used to detect circulating antibodies will be performed on sera derived from the pretreatment and post-cystectomy timepoints. After standard preprocessing of the protein array data, Cluster and Treeview software will be used for unsupervised clustering of the data with Pearson correlation and complete linkage. For each array, an antigen is identified as being detected if its value is above the median. To determine the number of up- and downmodulated antibodies, the difference in log2 intensity values of pretreatment and post-treatment samples will be taken for each patient to identify antigens that are detected differentially due to treatment. Number of antibodies with at least 2- or 4-fold difference between pretreatment and post-treatment samples will be compared between clinical responders and nonresponders by performing two-sided Wilcoxon rank sum test.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document.

The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the PI and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, however, the PI must then notify the IRB according to institutional requirements. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs at the site. The date, quantity and batch or code number of the drug, and the identification of participants to whom the investigational product has been dispensed by participant number and initials will be included.

The Principal Investigator at each participating site shall not make the investigational drug available to any individuals other than to qualified study participants. Furthermore, the PI at each study site will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, at each study site, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Study personnel for each study site will complete the CRFs; the PI for the study site will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by study personnel at each study site. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the PI at each study site is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The PI at each study site will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, and the trial statistician.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

The PI at each study site will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among Study Chair and the trial statistician.

9.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

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

9.9 Record Keeping and Record Retention

The PI at each study site is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The PI at each study site is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

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

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

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

9.10 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.11 Regulatory Documentation

Prior to implementing this protocol at UCSF or any participating site, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals
- Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Data and Safety Monitoring Plan: Multicenter Phase 2 or 3 Trial with Safety Lead-In

1.Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for auditing data quality and participant safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of all participant data in safety lead-in phase.
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair.
- Semiannual auditing after safety lead-in phase (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

2. Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the trial and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

All institutional Phase II or III therapeutic studies with a lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial.

After the completion of enrollment in the safety lead-in phase, the Study Chair will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the trial. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited by a DSMC Monitor/Auditor on a semiannual basis with a random selection of twenty percent of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.
Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All grade 3-5 adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution assignment from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.
UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business days of becoming aware of the event. The SAEs are reviewed and audited by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.
If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, then the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair (or Vice Chair) and the DSMC Director within 1 business day of this notification.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC Chair (or Vice Chair) and the DSMC Director at the time the increased rate is identified via a report. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.
If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

Data and Safety Monitoring Committee Contacts:

Katie Kelley, MD (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

John McAdams (DSMC Director)
[redacted]
UCSF HDFCCC
San Francisco, CA 94143

Appendix 3 Prohibited Medications

Drug	Trade name (if applicable)
Denosumab	Xgeva, Prolia
Interleukin-2	
Interferon gamma	Actimmune
Interferon alpha	Intron A, Roferon-A
Ipilimumab	Yervoy
Cyclophosphamide	Cytoxan
Azathioprine	Imuran, Azasan
Methotrexate	Trexall, Rheumatrex
Thalidomide	Thalomid
Dexamethasone*	
Prednisone*	
Methylprednisolone*	
Remicade	Infliximab
Etanercept	Enbrel
Adalimumab	Humira
Certolizumab	Cimzia
Golimumab	Simponi

*Inhaled corticosteroids are permitted. Systemic corticosteroids or anti-TNF-alpha agents are administered at the discretion of the treating physician after discussion with the Study Chair.

Appendix 4 TBNK, and Pharmacodynamic Sampling Schedule

Lab Correlative Sampling Schedule

Study Visit	Time	Sample
Screening	At visit	TBNK
Cycle 1, Day 1	Predose	TBNK Atezolizuab/Tiragolumab pharmacodynamics [a]
All subsequent cycles	Predose	TBNK Atezolizuab/Tiragolumab pharmacodynamics [a]
Treatment discontinuation visit	At visit	TBNK Atezolizuab/Tiragolumab pharmacodynamics [a]
At time of cystectomy & subsequent follow up visits, including any recurrence biopsy	*At Visit*	TBNK Atezolizuab and Tiragolumab pharmacodynamics [a]
12 weeks (± 2 weeks) after cystectomy	At visit	TBNK Atezolizuab/Tiragolumab pharmacodynamics [a]

PD = pharmacodynamic (plasma, serum, whole blood for PD biomarkers); TBNK = T, B, and NK cells.

[a] Plasma, serum, whole blood.

Refer to Laboratory Manual for additional sampling and shipping details.

Appendix 5 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 observations.

Appendix 6 Safety Reporting Fax Coversheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: [redacted]

Alternate Fax No: [redacted]

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: [redacted]

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Version 1 31-May-2012