A Phase II Trial of Atezolizumab and Bevacizumab in Cisplatin-ineligible Patients with Advanced/Unresectable Urothelial Cancer

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

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SYNOPSIS

TITLE	A Phase II Trial of Atezolizumab and Bevacizumab in Cisplatin-ineligible Subjects with Advanced/Unresectable Urothelial Cancer.
SHORT TITLE	Atezolizumab and Bevacizumab in Previously Untreated Metastatic/Unresectable Urothelial Cancer
PHASE	II
OBJECTIVES	Primary Objective: Overall Survival (OS) rate at 1 year Secondary Objectives: 1. Objective Response Rate (ORR) 2. Duration of Response (DoR) 3. Disease Control Rate (ORR + SD) 4. Progression-Free Survival (PFS) 5. Safety and Toxicity by CTCAE v4 Exploratory Objectives: 1.) Evaluation of frozen and FFPE tumor tissue and PBMCs/Sera from blood collected at baseline and on treatment will be interrogated to test the following immune hypotheses: • Immune Hypothesis 1: Bevacizumab counteracts the immunosuppressive functions of VEGF and favorably alters the ratio of effector to suppressor immune cells, allowing for unopposed anti-PD-L1 mediated T-cell activation. • Immune Hypothesis 2: Bevacizumab induces cancer cell death, release of tumor-associated antigens (TAAs), dendritic cell maturation, antigen presentation, and activation of tumor-specific T-cell clones. • Immune Hypothesis 3: PD-L1 expression is dynamic, increases with inflammation, and may increase following therapy with bevacizumab. Thus, anti-PD-L1 may abrogate adaptive resistance. • Immune Hypothesis 4: There is a genetic (tumor and host) basis for benefit from anti-PD-L1 blockade in bladder cancer. 2.) Collection of stool samples at baseline and on-treatment to perform metagenomic shotgun sequencing to characterize the microbial species present, targeted metabolomic assays, and bacterial culture. These analyses will power discoveries in: • Immune set point: Evaluating the impact of gut microbial heterogeneity on the development of T-cell driven anti-tumor immune responses. • Efficacy: Evaluating the gut composition of microbial species and metabolites present at baseline and the impact on response to therapy. • Safety: Evaluating how immunotherapy alters the gut microbiome and to test whether particular alterations contribute to the

	development of immune-related adverse side events (e.g. immune-related colitis).
STUDY DESIGN	This is a single arm phase II study assessing the activity of bevacizumab combined with atezolizumab in metastatic urothelial carcinoma subjects who are ineligible for cisplatin-based therapy. Eligible subjects will receive treatment with atezolizumab 1200 mg (flat dose) IV plus bevacizumab 15 mg/kg IV every 21 days. Cross-sectional imaging will be performed every 9 weeks on therapy for the first 12 months and then every 12 weeks thereafter to assess for response. Subjects will be eligible to continue treatment until RECIST v1.1 defined progression or unacceptable toxicity for up to 24 months. The primary endpoint will be OS rate at 1 year. Subjects will be required to submit untreated archival tumor tissue or undergo a pre-treatment core needle or excisional biopsy for biomarker analysis. Subjects must be willing to undergo repeat biopsy between Cycle 1 and Cycle 2 if deemed safe and feasible to assess for changes in immune-related biomarkers.
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. 2. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study 3. Age ≥ 18 years at the time of consent. 4. ECOG Performance Status of 0, 1 or 2 within 28 days prior to registration. 5. Histological or cytological evidence urothelial (transitional cell) carcinoma of the renal pelvis, ureter, bladder or urethra. 6. Locally advanced/unresectable disease as determined by site attending urologic oncologist or metastatic disease. 7. Evaluable untreated tumor tissue for biomarker analysis (25 unstained slides or FFPE tissue block). Subjects with < 25 slides may be enrolled after discussion with the sponsor-investigator. Untreated tumor tissue is defined as no intervening intravesical or systemic therapy since acquisition. Subjects without tissue available must be willing and safe to undergo biopsy repeat biopsy (core needle or excisional) prior to enrollment. 8. Willing to undergo a core needle or excisional biopsy on-treatment. Subjects will be assessed at the time of biopsy for safety of undergoing the procedure. 9. Measurable disease according to RECIST v1.1 within 28 days prior to registration. 10. No prior chemotherapy for locally advanced or metastatic urothelial cancer.

	• Perioperative chemotherapy previously administered in the neoadjuvant and/or adjuvant setting is permitted. • Prior chemotherapy administered in the context of chemoradiation as definitive treatment for bladder preservation is also permitted, provided that disease progression outside the prior radiotherapy field is demonstrated histologically or cytologically. 11. Ineligible for cisplatin as defined by presence of **one** or more of the following: • Impaired renal function (≤ 60 cc/min). GFR should be assessed by direct measurement (i.e. creatinine clearance or ethylenediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine by Cockroft-Gault equation. • Grade ≥ 2 hearing Loss (measured by loss of >25 dB at two contiguous frequencies in at least one ear for patients undergoing serial audiometry testing) • Grade ≥ 2 peripheral neuropathy • ECOG Performance Status of 2 • Solitary Kidney • Refusing Cisplatin-based chemotherapy 12. If palliative radiotherapy administered, completion of palliative radiation therapy must be ≥ 2 weeks prior to Cycle 1 Day 1 of protocol therapy. 13. Demonstrate adequate organ function as defined in the table below. All screening labs must be obtained **within 14 days** prior to Cycle 1 Day 1 of treatment. • Absolute Neutrophil Count (ANC) ≥ 1,000 K/mm3 • Hemoglobin (Hgb) ≥ 9.0 g/dL • Absolute Lymphocyte count ≥ 500/uL • Platelet Count ≥ 100,000/uL • Serum Creatinine < 2.5 or Calculated creatinine clearance ≥ 25 cc/min using a direct method or the Cockcroft-Gault formula • Urinary Protein Excretion < 1.0 g/24 hours (as estimated by urine protein-creatinine ratio) • Bilirubin ≤ 1.5 × upper limit of normal (ULN) (subjects with known Gilbert's disease who have serum bilirubin ≤ 3.0 x ULN may be enrolled) • Aspartate aminotransferase (AST) ≤ 2.5 × ULN (5.0 x ULN if Liver involvement) • Alanine aminotransferase (ALT) ≤ 2.5 × ULN (5.0 x ULN if Liver involvement) • Serum Album ≥ 2.5 g/dL • International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 × ULN (Note: This applies only to subjects who are not receiving

	therapeutic anticoagulation; subjects receiving therapeutic anticoagulation should be on a stable dose) 14. Females of childbearing potential must have a negative serum pregnancy test within 28 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. 15. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 150 days (5 months) after discontinuation of atezolizumab and until 180 days (6 months) after discontinuation of bevacizumab. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method. **Exclusion Criteria** 1. Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment; the following exceptions are allowed: • Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging • Hormone-replacement therapy or oral contraceptives 2. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to enrollment 3. Active or untreated CNS metastases or leptomeningeal disease as determined by CT or MRI evaluation during screening and prior radiographic assessments. 4. Subjects with treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria: • Evaluable or measurable disease outside the CNS • No metastases to midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm) • No history of intracranial or spinal cord hemorrhage • No evidence of significant vasogenic edema • No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose allowed • No stereotactic radiation, whole-brain radiation within 4 weeks prior to Cycle 1 Day 1 • Subjects with CNS metastases treated by neurosurgical resection or brain biopsy within 3 months prior to Cycle 1 Day 1 will be excluded. • Radiographic demonstration of interim stability (i.e., no progression) between the completion of CNS-directed therapy and the screening radiographic study

	• Screening CNS radiographic study ≥ 4 weeks since completion of radiotherapy or surgical resection and ≥ 2 weeks since discontinuation of corticosteroids 5. Uncontrolled tumor-related pain. **NOTE:** Subjects requiring pain medication must be on a stable regimen at study entry. 6. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) 7. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. **NOTE:** Patients with asymptomatic hypercalcemia controlled with medical therapy are eligible. 8. Subjects who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible. 9. Subjects who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study. 10. Malignancies other than urothelial cancer within 5 years prior to Cycle 1 Day 1, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (T1/T2a, Gleason score ≤ 3 + 4, and PSA ≤ 0.5 ng/mL undergoing active surveillance and treatment naive). 11. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study). 12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins. 13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab or bevacizumab formulation. 14. 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 anti-phospholipid syndrome, granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. 15. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. 16. Subjects with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.

	17. Subjects with a history of celiac disease may be eligible if controlled with diet. 18. 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 19. History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 20. History of confirmed positive test for HIV. 21. Subjects with active hepatitis B virus (HBV) (chronic or acute, defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C virus (HCV) 22. Subjects with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. 23. Subjects positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA. 24. Active tuberculosis 25. 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 26. Signs or symptoms of active infection within 2 weeks prior to Cycle 1 Day 1 27. Received therapeutic oral or IV antibiotics within 1 week prior to Cycle 1 Day 1 28. Subjects receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible. 29. Significant cardiovascular disease, such as: • New York Heart Association Congestive Heart Failure Class II or greater • Myocardial infarction, unstable angina or unstable arrhythmias within 3 months of enrollment. • History of stroke or TIA within 3 months of enrollment • Other clinically significant arterial vascular disease within 6 months of enrollment (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis). Prior history of adequately treated venous thromboembolism > 7 days prior to C1D1 on stable dose of therapeutic anticoagulation is permitted • Subjects 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.

	30. 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 during the course of the study 31. Prior allogeneic stem cell or solid organ transplant 32. 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. 33. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications **Atezolizumab-Specific Exclusion Criteria** 1. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies. 2. Prior cancer vaccines and cellular immunotherapy are permitted. 3. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, interleukin [IL]-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1 Day 1 4. 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 5. Subjects who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled. 6. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency) is allowed. **Bevacizumab-Specific Exclusion Criteria** 1. Inadequately controlled hypertension (defined as persistent systolic blood pressure (SBP) > 150 and/or diastolic blood pressure (DBP) > 100 mmHg) 2. Prior history of hypertensive crisis or hypertensive encephalopathy 3. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation) 4. Current or recent (within 10 days of study enrolment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), or current or recent (within 10 days prior to first dose of bevacizumab) use of therapeutic oral or parenteral anticoagulants or thrombolytic agents for therapeutic

	purposes. **NOTE:** The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the institution) and the subject has been on a stable dose of anticoagulants for at least two weeks at the time of study enrollment. Prophylactic use of anticoagulants is allowed. 5. History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month of study enrollment. 6. Minor surgical procedure within 7 calendar days prior to Cycle 1 Day 1 7. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to enrollment 8. Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding 9. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure 10. Serious non-healing or dehiscing wound, active ulcer, or untreated or non-healing bone fracture 11. On-going gross hematuria associated with clots
STATISTICAL CONSIDERATIONS	Following an FDA safety alert and update to prescriber information for single agent atezolizumab in unselected first-line patients, we have redesigned the study to be single arm binomial design of atezolizumab and bevacizumab combination therapy. We will accrue 70 patients to the atezolizumab and bevacizumab arm and the primary endpoint will be 1 year overall survival, where 57% 1 year OS is considered the null rate, and 72% 1 year OS as desirable rate. If 46 patients or more are alive at 1 year, the treatment will be deemed promising. This design has 10% type 1 error and 90% power. The primary endpoint will be analyzed as a binary endpoint when all alive patients have at least 1 year of follow-up. As a secondary analysis overall survival will be analyzed as a time to event endpoint using the Kaplan Meier method. Overall survival will be defined as the time from treatment initiation until death by any cause. At the time of analysis, if a subject has not died, the subject will be censored on the date of last follow-up.
TOTAL NUMBER OF SUBJECTS	N = 70
ESTIMATED STUDY TIMEFRAMES	Estimated enrollment period: 25 months Estimated study duration 43 months

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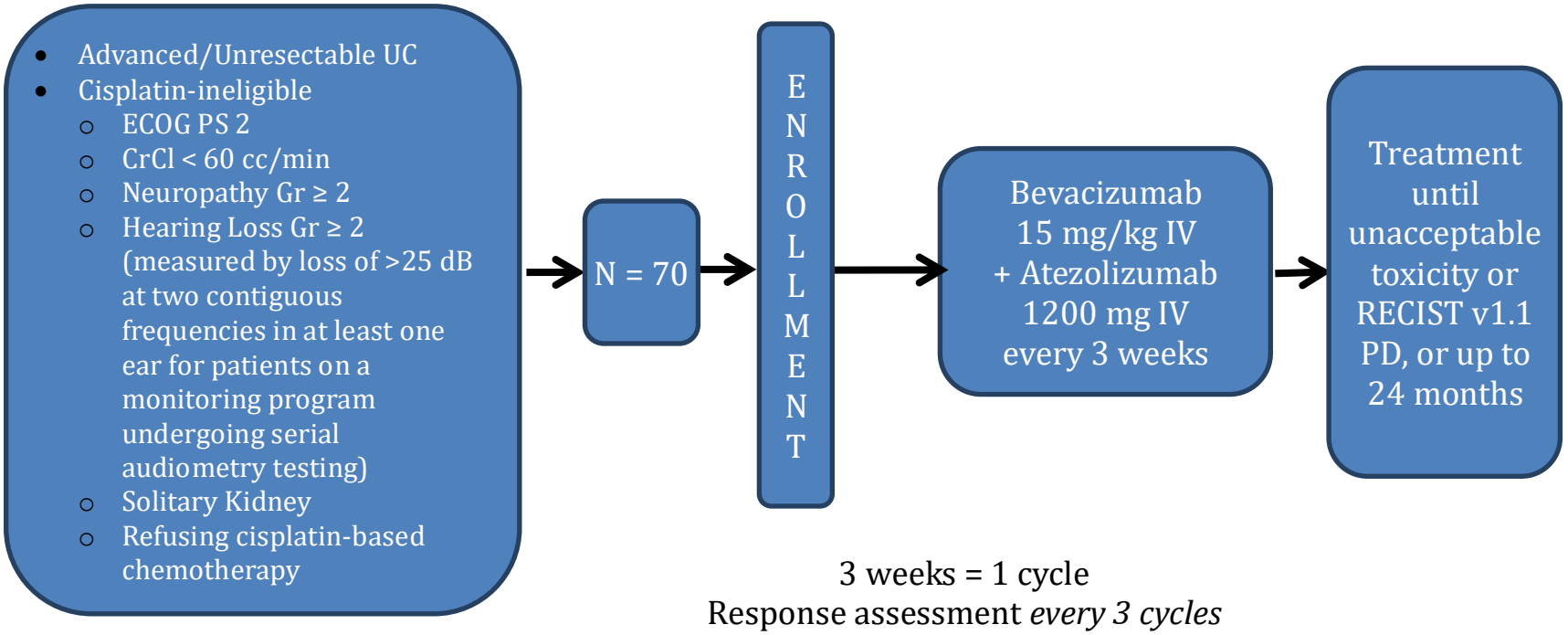
SCHEMA



Subjects will undergo on-treatment tumor biopsy if deemed safe and feasible between Cycle 1 and Cycle 2 of therapy.

1. Background and Rationale

Urothelial carcinoma (UC) of the urinary bladder is the second most common genitourinary malignancy. Each year in the United States, more than 70,000 patients will develop urothelial cancer and over 14,000 will die of their disease.[1] While UC is a chemotherapy sensitive disease, current therapeutic approaches are inadequate. Response durations are short and the median survival of patients with metastatic disease approximately 12-15 months with cisplatin-based chemotherapy, outcomes which have remained unchanged for over 30 years.[2] These findings highlight the need for novel approaches to the treatment of metastatic UC.

1.1 Proportion of Cisplatin Ineligible Patients

Cisplatin-based combination chemotherapy is considered the standard of care for patients with locally advanced or metastatic UC, and is the only therapy ever shown to improve survival in any urothelial cancer disease state. However, a large proportion of patients are ineligible for such treatment based on renal function or disease/functional status. In a retrospective study of 512 patients with UC who were candidates for adjuvant chemotherapy based on pathologic stage (≥ T3 and/or node positive), 40% were ineligible for cisplatin-based therapy due to a calculated creatinine clearance of < 60 ml/min alone – in patients > 60 years old, 63% were ineligible.[3] The median age of diagnosis of advanced bladder cancer is 70, and the proportion of cisplatin-ineligible patients is expectedly higher in the metastatic disease population.

Independent of renal function, many patients are also considered ineligible for cisplatin-based therapy due to concerns of excessive treatment-related toxicity, in particular for patients felt to be incurable with cisplatin. This has led many oncologists to utilize cisplatin-based therapy only in a select subgroup of patients (young patients, lymph node only metastases).[4] The optimal definition of ineligibility for cisplatin-based therapy has been debated and inconsistent across clinical trials. This culminated in an effort to derive a consensus definition of cisplatin ineligibility for clinical trials. Ineligibility for cisplatin was defined as any of the following: 1.) ECOG PS 2 (KPS 60-70%); 2.) Calculated Creatinine Clearance < 60 cc/min; 3.) Grade ≥ 2 hearing loss; 4.) Grade ≥ 2 peripheral neuropathy; 5.) New York Heart Association Class III heart failure.[5,6] Similarly, the renal safety of cisplatin in the context of a solitary kidney is not well-established and therefore represents another criterion that may define ineligibility for cisplatin. In a phase II study of gemcitabine, carboplatin and bevacizumab in cisplatin-ineligible patients with metastatic urothelial cancer, patients with a history of a solitary kidney were eligible.[7] Post-hoc analysis demonstrated that 14 of 15 patients enrolled with a solitary kidney also had impaired renal function (estimated GFR < 60 cc/min) suggesting these patients should similarly be considered ineligible for cisplatin.[7]

1.2 Standard Therapy for Cisplatin Ineligible Patients

Carboplatin-based therapy is considered a standard option in cisplatin-ineligible patients however is inferior to cisplatin.[8-12] Therefore, carboplatin-based chemotherapy has been an accepted community standard reserved for cisplatin-ineligible patients and only recently did a phase III trial establish level 1evidence for a treatment regimen for cisplatin-ineligible patients. EORTC 30986 was a phase II/III trial of Gemcitabine and

Carboplatin versus Methotrexate, Carboplatin and Vinblastine (M-CAVI) that demonstrated a response rate of 41.2%, median TTP of 5.8 months and median overall survival of 9.3 months with gemcitabine and carboplatin and 30.3% RR, 4.2 months median TTP and 8.1 months median OS with M-CAVI.[13] Therapy with gemcitabine and carboplatin was better tolerated than M-CAVI and thus, established the first level one evidence for the use gemcitabine and carboplatin in cisplatin-ineligible patients. However, data from this trial failed to demonstrate a survival benefit for either regimen, and further underscores the poor survival for cisplatin-ineligible patients and desperate need to develop novel, better tolerated and more efficacious therapies. Currently, there are no FDA approved therapies for cisplatin-ineligible patients with metastatic urothelial cancer.

1.3 Immune Checkpoint Inhibition as Cancer Therapy

In conjunction with an enhanced understanding of tumor and host immune system interactions, immunotherapeutic strategies have recently reemerged as a promising approach for cancer therapy. Recognition that T-cell activation involves the engagement of both co-stimulatory and co-inhibitory signals and that these signals can be co-opted by tumors as a mechanism of immune evasion has led to the clinical development of therapies aimed at attenuating these co-inhibitory signals.

This novel class of immune therapies, broadly termed immune-checkpoint inhibitors, has demonstrated significant and durable activity in a number of solid tumor malignancies, beginning first with ipilimumab in advanced melanoma. Ipilimumab is a monoclonal antibody that blocks CTLA (cytotoxic T-lymphocyte antigen)-4, a co-inhibitory receptor expressed on CD8+ T-cells during T-cell priming and down-regulates T-cell function. CTLA-4 is activated upon binding with B7-1/2 expressed on antigen presenting cells shortly after presentation of MHC Class I antigen complex for binding to the T-cell receptor (TCR), and functions to prevent the development of antigen-specific effector T-cells. By blocking CTLA-4, ipilimumab enhances T-cell priming and was shown to improve survival over gp100 vaccine in a phase III trial in advanced melanoma, leading to FDA approval.[14]

More recently, therapies targeting immune checkpoints expressed on effector T-cells have demonstrated even more promising activity. PD-1 is a co-inhibitory receptor expressed on activated (effector) T-cells and down-regulates T-cell function upon binding with its ligands PD-L1 or PD-L2, which are commonly overexpressed on cancer cells as well as certain suppressive immune cells. Antibodies blocking PD-1 signaling have also demonstrated significant and durable activity in solid tumors, and efficacy is further augmented when added to CTLA-4 blockade, confirming that stimulation of both T-cell priming and effector functions enhances antitumor immunity.[15, 16] Due to the role of PD-1 in suppressing effector T-cell functions, pre-existing anti-tumor immunity is required for the efficacy of PD-1/PD-L1 blocking antibodies.

1.4 PD-L1 Targeted Therapy in Advanced Urothelial Cancer (UC)

1.4.1 Atezolizumab (Anti-PD-L1)

Atezolizumab (MPDL3280A) is an anti-PD-L1 blocking antibody currently in clinical development in a variety of solid tumor malignancies, including urothelial cancer. Atezolizumab is a human IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death−ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death−1 (PD-1) and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

1.4.2 Atezolizumab is Active and Well-Tolerated in Advanced Urothelial Cancer

Recently reported data from two phase I trials of PD-1/PD-L1 blocking antibodies in previously treated metastatic urothelial patients demonstrated rapid and durable responses and favorable tolerability compared to cytotoxic chemotherapy, warranting further testing in larger studies.[17, 18] Specifically, PCD4989g was a phase Ia trial of atezolizumab (MPDL3280A; PD-L1 blocking antibody) which included multiple tumor types, including metastatic urothelial bladder cancer. Probability of response was associated with baseline PD-L1 expression on tumor-infiltrating immune cells (IC), categorized by IC0 (absent or < 1% expression); IC1 (low expression, ≥1% but < 5%); IC2 (moderate expression; ≥5% but < 10%) and IC3 (high expression; ≥ 10%) by SP142, an anti-PD-L1 specific and sensitive Rabbit Monoclonal Primary Antibody IHC system.

As of the clinical data cutoff of December 2, 2014, the safety evaluable population included 92 patients with locally advanced or metastatic UBC. Efficacy analyses were performed on 15 IC0, 26 IC1, 34 IC2, and 12 IC3 efficacy evaluable patients (N = 87) with locally advanced or metastatic urothelial bladder cancer (UBC) who were followed for a minimum of 12 weeks.

The median age of the safety evaluable population was 66 years (range: 36-89 years) and represented a heavily pre-treated patient population: 89 patients (96.7%) had received ≥2 prior therapies and 60 patients (65.2%) had received at least 4 prior therapies. There were 86 patients (93.5%) who had received prior platinum-based chemotherapy.

Responses were observed in all PD-L1 subgroups (Table 1a and 1b), with higher ORRs associated with higher PD-L1 expression in IC. The median duration of response (confirmed) as assessed by investigator per RECIST v1.1 was 15.2 months (95% CI: 11.3, 16.9) for IC2/3 patients, and has not yet been reached for IC0/1 patients (95% CI: 6.2, NE). Seventeen of the twenty-four responding patients had ongoing responses at the time of data cutoff.

1.4.3 Table 1a. Efficacy of Atezolizumab in UC Patients Enrolled in PCD4989g

IC Score	ORR (95% CI)
IC 3	66.7% (35% - 90.1%)
IC 2	44.1% (27.2% - 62.1%)
IC 1	19.2% (6.55% - 39.35%)
IC 0	13.3% (1.66% - 40.46%)

CI = confidence interval; IC = PD-L1 positive tumor-infiltrating immune cells; ORR = objective response rate

Based on these promising data, atezolizumab was granted break-through designation in metastatic urothelial cancer by the United States FDA and led to IMVigor210 (GO29293), which is a phase II trial of single agent atezolizumab in patients with unresectable or metastatic urothelial cancer. A fixed dose of 1200 mg IV (equivalent to an average body weight-based dose of 15 mg/kg) was chosen on the basis of both non-clinical and available clinical data from PCD4989g.

IMvigor210 enrolled two patient cohorts: Cohort 1 enrolled 119 previously untreated metastatic urothelial cancer patients ineligible for cisplatin-based therapy and Cohort 2 enrolled 311 patients who had previously received and progressed during or following platinum-based combination therapy with no restriction on number of prior lines of therapy. The primary endpoint was ORR (central and investigator-assessed) by RECIST v1.1 and results of the primary efficacy analysis for cohort 2 were recently presented at the 2015 European Cancer Congress (Table 2).[19] Patients with IC2/3 PD-L1 expression had an ORR of 27%, IC1 had an ORR of 10% and IC0 had an ORR of 9%. Notably, at a median follow up of 7 months, 92% of responses were ongoing with a median DoR not reached in any IC subgroup.

1.4.4 Table 1b. Efficacy of Atezolizumab in UC patients Enrolled in IMvigor 210

	RECIST v1.1 Criteria by Independent Review[a]				
PD-L1 subgroup	**N**	**CR (%)**	**ORR (%)**	**95% CI**	***P* value**[b]
IC2/3	100	**8%**	**27%**	19, 37	< .0001
IC1/2/3	208	**5%**	**18%**	13, 24	.0004
All	311	**4%**	**15%**	11, 20	.0058
IC1	108	3%	10%	5, 18	N/A[c]
IC0	103	1%	9%	4, 16	N/A[c]

[a]Objective response evaluable population: all treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1.

[b]*P*-value for H_o: ORR = 10% versus H_a: ORR ≠ 10%, where 10% ORR is historical control, $\alpha = 0.05$.

[c]No formal hypothesis testing conducted. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Cohort 1 of IMVigor 210 was recently presented at the ASCO Annual Meeting in 2016 and published in *The Lancet* in 2017. At a median follow up of 17.2 months, ORR for atezolizumab was 23% (9% CR rate) for the 119 patients enrolled. Responses were observed in all PD-L1 IC subgroups, including 21% of patients with IC0 expression.

Twenty-eight percent of patients with IC2/3 expression achieved an objective response. At the time of data cut-off and median follow up of 17.2 months, 70% (19 of 27) of responses were on-going and the estimated median survival was 15.9 months (95% CI 10.4 to not estimable). The land-mark 1 year OS rate was 57%.

Based on the currently available data re: efficacy of atezolizumab in advanced urothelial cancer, it appears that only a subset of patients respond to therapy, with higher PD-L1 expression in tumor infiltrating immune cells associated with a higher probability of response. Furthermore, an FDA issued safety alert in May 2018 identified shorter survival for PD-L1 low/negative expressing patients treated with first-line immunotherapy compared to platinum-based (carboplatin or cisplatin) chemotherapy in two randomized phase III trials (IMVigor 130 and KEYNOTE-361), leading the FDA in July 2018 to modify the prescriber label for atezolizumab to restrict first-line use to cisplatin-ineligible patients with IC2/3 (5% expression or greater on immune-cells) or to those patients who are not eligible for any platinum-based chemotherapy including carboplatin. Additional strategies to enhance anti-tumor immunity by targeting immune-suppressive mechanisms are warranted to improve the efficacy of anti-PD-L1 targeted treatment.

1.5 VEGF Mediates Immune Suppression in Tumor Microenvironment

VEGF and VEGF receptor signaling has previously been known to induce proliferation of mature endothelial cells and formation of tumor neovasculature. Further, VEGF over-expression has also been associated with a poor prognosis in multiple cancers, including urothelial cancer.[20-22] VEGF receptor expression is common on early hematopoietic progenitors and has been shown to have broad effects on the maturation of immune cell populations.[23] Specifically, VEGF causes a defect in the functional maturation of dendritic cells (DC) from progenitors, which appears to be associated with impaired activation of NF-kappaB.[24] In pre-clinical and clinical tumor models, increased VEGF expression is associated with impaired antitumor immune responses, including the suppression of DC maturation, increased in tumor levels of immunosuppressive cell populations such as FOXP3+ regulatory T cells and myeloid-derived suppressor cells (MDSCs), and is also associated with inhibition of functional T-cell responses.[25-30] Increased baseline serum VEGF levels have been correlated to lower likelihood of response and decreased survival in advanced melanoma patients treated with ipilimumab.[31] Therapeutic inhibition of VEGF may abrogate VEGF-mediated immunosuppression. Further, there is evidence for synergy between anti-PD-L1 and anti-VEGF therapies in preclinical models (Genentech, Inc, data on file).

1.6 Therapeutic Inhibition of VEGF Enhances Antitumor Immunity in combination with CTLA-4 Blockade a Phase I Trial.

Immune correlates from a phase I study of bevacizumab added to ipilimumab suggests enhancement of antitumor immunity.[32, 33] Forty-six patients with metastatic melanoma were treated in four dosing cohorts of ipilimumab (3 or 10mg/kg) with four doses at 3-week intervals and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks. On-treatment tumor biopsies revealed activated vessel endothelium including morphologic changes in intratumoral endothelia with rounded and columnar CD31+ cells

compared with pretreatment or post-treatment samples from patients receiving ipilimumab alone.

With pathologic examination of immune infiltrates associated with treatment, significant trafficking of $CD8^+$ T cells and $CD163^+$ dendritic macrophages across the tumor vasculature was witnessed in ipilimumab plus bevacizumab post-treatment biopsies that were qualitatively increased in comparison with that elicited by ipilimumab alone. Peripheral blood analyses demonstrated increases in $CCR7^{+/-}/CD45RO^+$ cells and anti-galectin antibodies. Best overall response included 8 partial responses, 22 instances of stable disease, and a disease-control rate of 67.4%. Median survival was 25.1 months. Bevacizumab was shown to influence changes in tumor vasculature and immune responses with ipilimumab administration. This study showed that the combination of bevacizumab and ipilimumab could be safely administered and also revealed that the addition of VEGF-A blockade can further influence inflammation, lymphocyte trafficking, and immune regulation.

1.7 VEGF-Targeted Therapies are Active in Advanced UC.

Multiple lines of pre-clinical and clinical lines of evidence support targeting angiogenesis in UC.[34-43] A phase II trial of sunitinib in pre-treated advanced UC patients first demonstrated the VEGF-axis as a viable target for the development of novel UC therapies.[44] A phase II trial of bevacizumab added to gemcitabine and carboplatin in cisplatin-ineligible/incurable patients demonstrated a median PFS of 6.5 months and median OS of 13.9 which compared favorably to historical controls (Table 2).[45, 46] Furthermore, nine of 28 patients who received maintenance bevacizumab on this study experienced continued tumor regression, suggesting potential benefit to single-agent therapy. A similar study in cisplatin-eligible patients also demonstrated promising response and survival outcomes[47] and a large phase III trial of gemcitabine and cisplatin with or without bevacizumab in advanced UC (CALGB/Alliance 90601 (NCT00942331); PI: Jonathan Rosenberg MD) recently completed accrual. The primary endpoint of this study was overall survival and results are eagerly anticipated.

Table 2.

Comparison of Platinum-Gemcitabine Plus Bevacizumab vs Historical Controls (Platinum-Gem)				
	HOG-04-75 GCis + Bev (N=43)	(Historical Controls)[48, 49] GCis	**MSKCC GCa + Bev (N=47)**	(Historical Controls)[46] GCa
Response Rate (PR + CR)	**72%**	50-60%	**49%**	40 – 45%
Median PFS	**8.2 months**	7 – 8 months	**6.5 months**	4.8 – 5.8 months
Median OS	**19.1 months**	12-15 months	**13.9 months**	7 – 9 months

1.8 Bevacizumab added to Atezolizumab is Active and Well-Tolerated in Metastatic Renal Cell Carcinoma in a Phase Ib trial

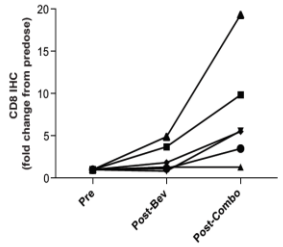
In a phase Ib study of bevacizumab added to atezolizumab in 10 previously untreated metastatic renal cell carcinoma patients, therapy was well tolerated and there was evidence of clinical benefit.[50] Patients on this trial were treated with atezolizumab 20 mg/kg IV with bevacizumab 15 mg/kg IV every 3 weeks. Treatment was well tolerated

with 6 total Grade 3-4 adverse events reported, none felt to be possibly related to study treatment. The most common adverse events reported were fatigue, decrease appetite, arthralgia and nausea.

In the first cycle, patients on this study were treated first with single agent bevacizumab, with subsequent on-treatment tumor biopsy, followed by combination therapy, and another on-treatment biopsy with the aim to study the sequential effects of single agent bevacizumab and then combination therapy on the tumor microenvironment. Six patients successfully underwent on-treatment biopsies which demonstrated increases in CD8+ T-cell infiltrates with single agent bevacizumab compared to baseline, which further increased with combination therapy suggesting synergy between these two therapies (Figures 1 and 2 below).

Figure 1

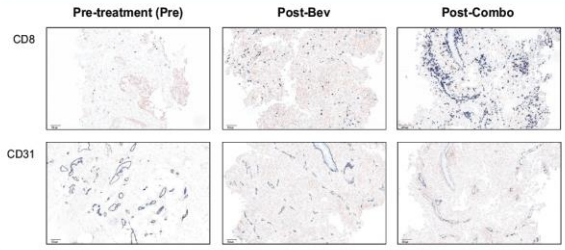
Figure CD8 Staining in the Tumors of Patients With RCC After Treatment With MPDL3280A + Bevacizumab



IHC, immunohistochemistry.

Figure 2

Figure CD8+ Cell Prevalence Before and After Treatment in a Patient With RCC

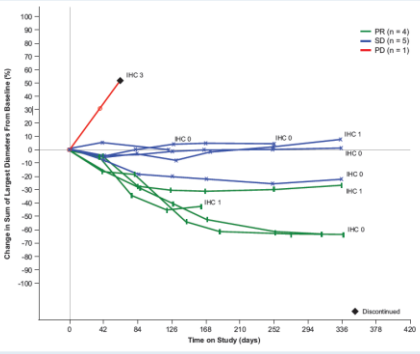


CD31, also known as platelet endothelial cell adhesion molecule-1, serves as a marker of endothelial cells.

Although this study enrolled only 10 patients with a primary endpoint of safety and tolerability, there was evidence of clinical benefit with this treatment. The objective response rate in 10 evaluable patients was 40%, with an additional 5 patients (50%) achieving stable disease (Figure 3).

Figure 3

Figure Tumor Burden Over Time in Patients With RCC



In a phase Ib study of single agent atezolizumab in advanced RCC the ORR was 15%, and the observed ORR for bevacizumab monotherapy in advanced RCC is 10%.[51, 52] These data provided justification to test this combination in larger studies powered to test efficacy, leading to phase II (NCT01984242; IMmotion150) and phase III (NCT02420821; IMmotion151) randomized studies of bevacizumab plus atezolizumab

versus sunitinib in advanced renal cell carcinoma. IMmotion150 recently completed accrual and data are expected to be presented soon.

1.9 Bevacizumab Clinical Experience in Other Malignancies

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 22,000 patients and in multiple tumor types. Approximately 1,720, 000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.
In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.66 ($p < 0.001$) and a median survival of 20.3 vs. 15.6 months. Similar increases were seen in progression-free survival (10.6 vs. 6.2 months; HR 0.54, $p < 0.001$), overall response rate (34.8% vs. 44.8%; $p = 0.004$) and duration of response (10.4 vs. 7.1 months; HR 0.62, $p = 0.001$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, November 2012). Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

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

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

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

carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006.

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

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

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

1.10 Study Rationale

PD-1/L1 blocking antibodies are an active and well-tolerated class of immunotherapy in advanced/metastatic urothelial cancer however activity appears to be limited to a subset of patients. Cisplatin ineligible patients received treatment with atezolizumab on the phase II trial IMVigor210 cohort 1. In this cohort, patients demonstrated an objective response of 24% and median overall survival of 15.9 months[57]. Resistance to PD-1/L1 blocking antibodies is likely multifactorial and includes factors such as impaired dendritic cell maturation/function, infiltration of immunosuppressive populations such as T-Regs and MDSCs, impaired T-cell priming leading to absence of tumor-specific

effector T-cells and impaired T-cell trafficking in tumors. Therapies aimed to address these defects in the immune response may synergize well with PD-1/L1 blocking antibodies and improve outcomes.

The current phase II trial of atezolizumab combined with bevacizumab in previously untreated cisplatin-ineligible patients with locally advanced/unresectable or metastatic urothelial cancer is supported by the following rationale:

- Atezolizumab is an FDA approved therapy for treatment of cisplatin ineligible urothelial cancer.
- Bevacizumab has demonstrated activity in advanced urothelial cancer based on data from two phase II studies of bevacizumab with chemotherapy, including possible evidence of single agent activity.
- Blockade of VEGF signaling with bevacizumab has broad effects on the tumor microenvironment including:
    - Blockade of VEGF-mediated angiogenesis and normalization of vasculature which may improve delivery of systemic therapy and also improve T-Cell trafficking into tumors.
    - Blockade of VEGF-mediated immunosuppression may improve dendritic cell maturation and function, and reduce tumor levels of T-Regs and MDSCs.
    - Blockade of VEGF-mediated immunosuppression may also promote T-cell and dendritic cell trafficking and also induce peripheral memory T-cell expansion
- Atezolizumab plus Bevacizumab is a well-tolerated regimen in patients with metastatic renal cell carcinoma in a phase Ib trial with evidence of synergistic activity, leading to two randomized phase II (NCT01984242; IMmotion150) and III (NCT02420821; IMmotion151) studies in metastatic renal cell carcinoma.
- Atezolizumab plus bevacizumab may improve outcomes in advanced urothelial cancer and is a logical candidate for further study in a prospective trial.

1.11 Rationale for Dose and Schedule for Atezolizumab and Bevacizumab

Several lines of evidence support the dose and schedule of therapy proposed in this study. These include data during the initial development of atezolizumab (MPDL3280A) in the first phase Ia trial (Study PCD4989b) and non-clinical studies which supported the development of 1200 mg IV flat dosing (equivalent to an average body weight-based dose of 15 mg/kg) every 3 weeks. Subsequently, on-going phase II and III trials of atezolizumab monotherapy in urothelial cancer have demonstrated the safety and activity at the 1200 mg IV flat dose every 3 weeks schedule. Cohort 1 from the IMvigor210 study which selected 119 patients who match the current protocol population were treated with single-agent atezolizumab 1200 mg IV every 21 days.

For combination therapy in this study, a phase Ib study of bevacizumab 15 mg/kg IV plus atezolizumab 1200 mg IV (flat dose) every 3 weeks in advanced renal cell carcinoma also demonstrated safety and activity of this regimen.[50] These data supported the development of randomized phase II and III trials of atezolizumab 1200 mg IV plus bevacizumab 15 mg/kg IV every 3 weeks in advanced renal cell carcinoma which have been recently reported.

1.12 Rationale for the primary endpoint

Immune checkpoint inhibitors as a class of cancer therapy work via unique mechanisms whereby patients who achieve a response to therapy are likely to benefit long-term including the possibility for long-term survival. For patients with advanced urothelial cancer treated with atezolizumab, results from the primary analysis from cohort 2 of IMVigor210 demonstrated that while the ORR was 15% in the 311 patients treated, 92% (43 of 47 patients) of responses were on-going at the time of data cut-off at a median follow up of 7 months. Similarly, patients who achieve stable disease long-term may similarly continue to derive long-term clinical benefit. Lastly, even in patients who do not achieve a response or stable disease, immunotherapy may still enhance existing anti-tumor immunity thereby slowing disease progression and leading to extension of survival without evidence of objective radiographic response or prolongation of progression-free survival.[53]

Therefore, endpoints such as objective response rate and progression-free survival may not adequately capture the clinical activity of PD-L1 blocking antibodies in metastatic urothelial cancer. In this study we propose a primary endpoint of landmark overall survival rate which may more accurately capture the activity and clinical benefit of anti-PD-L1 antibody therapy in advanced urothelial cancer with the objective of testing whether combination atezolizumab plus bevacizumab improves on the landmark overall survival rate historically observed with atezolizumab alone. Overall survival rate at 1 year was chosen based on the currently available survival data from the phase Ia PCD4989g study as well as the expected median survival of 9 – 10 months for cisplatin-ineligible patients treated with standard carboplatin-based therapy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- Estimate the 1 year overall survival rate for atezolizumab plus bevacizumab treatment in cisplatin-ineligible subjects with locally advanced/unresectable and metastatic urothelial cancer.

2.1.2 Secondary Objectives

- Estimate the Objective Response Rate (ORR)
- Estimate the Duration of Response (DoR)
- Estimate the Disease Control Rate (ORR + SD)
- Estimate the Progression-Free Survival (PFS)
- Describe the Safety and Toxicity by CTCAE v4

2.1.3 Correlative/Exploratory Objectives

- Evaluation of frozen and FFPE tumor tissue and PBMCs/Sera from blood collected at baseline and on treatment will be interrogated to test the following immune hypotheses:
    - Immune Hypothesis 1: Bevacizumab counteracts the immunosuppressive functions of VEGF and favorably alters the ratio of effector to suppressor immune cells, allowing for unopposed anti-PD-L1 mediated T-cell activation.
    - Immune Hypothesis 2: Bevacizumab induces cancer cell death, release of tumor-associated antigens (TAAs), dendritic cell maturation, antigen presentation, and activation of tumor-specific T-cell clones.
    - Immune Hypothesis 3: PD-L1 expression is dynamic, increases with inflammation, and may increase following therapy with bevacizumab. Thus, anti-PD-L1 may abrogate adaptive resistance.
    - Immune Hypothesis 4: There is a genetic (tumor and host) basis for benefit from anti-PD-L1 blockade in bladder cancer.
- Collection of stool samples at baseline and on-treatment to perform metagenomic shotgun sequencing to characterize the microbial species present, targeted metabolomic assays, and bacterial culture. These analyses will power discoveries in:
    - Immune set point: Evaluating the impact of gut microbial heterogeneity on the development of T-cell driven anti-tumor immune responses.
    - Efficacy: Evaluating the gut composition of microbial species and metabolites present at baseline and the impact on response to therapy.
    - Safety: Evaluating how immunotherapy alters the gut microbiome and to test whether particular alterations contribute to the development of immune-related adverse side events (e.g. immune-related colitis).

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

3. Age ≥ 18 years at the time of consent.

4. ECOG Performance Status of 0, 1 or 2 within 28 days prior to registration.

5. Histological or cytological evidence urothelial (transitional cell) carcinoma of the renal pelvis, ureter, bladder or urethra.

6. Locally advanced/unresectable disease as determined by site attending urologic oncologist or metastatic disease.

7. Evaluable untreated tumor tissue for biomarker analysis (25 unstained slides or FFPE tissue block). Subjects with < 25 slides may be enrolled after discussion with the sponsor-investigator. Untreated tumor tissue is defined as no intervening intravesical or systemic therapy since acquisition. Subjects without tissue available must be willing and safe to undergo biopsy repeat biopsy (core needle or excisional) prior to enrollment.

8. Willing to undergo a core needle or excisional biopsy on-treatment. Subjects will be assessed at the time of biopsy for safety of undergoing the procedure.

9. Measurable disease according to RECIST v1.1 within 28 days prior to registration.

10. No prior chemotherapy for locally advanced or metastatic urothelial cancer.
    - Perioperative chemotherapy previously administered in the neoadjuvant and/or adjuvant setting is permitted.
    - Prior chemotherapy administered in the context of chemoradiation as definitive treatment for bladder preservation is also permitted, provided that disease progression outside the prior radiotherapy field is demonstrated histologically or cytologically.

11. Ineligible for cisplatin as defined by presence of **one** or more of the following:
    - Impaired renal function (≤ 60 cc/min). GFR should be assessed by direct measurement (i.e. creatinine clearance or ethylenediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine by Cockroft-Gault equation.
    - Grade ≥ 2 hearing Loss (measured by loss of >25 dB at two contiguous frequencies in at least one ear for patients undergoing serial audiometry testing)
    - Grade ≥ 2 peripheral neuropathy
    - ECOG Performance Status of 2
    - Solitary Kidney
    - Refusing Cisplatin-based chemotherapy

12. If palliative radiotherapy administered, completion of palliative radiation therapy must be ≥ 2 weeks prior to Cycle 1 Day 1 of protocol therapy.

13. Demonstrate adequate organ function as defined in the table below. All screening labs must be obtained **within 14 days** prior to Cycle 1 Day 1 of treatment.

System	Laboratory Value
Hematological	
Absolute Neutrophil Count (ANC)	≥ 1,000 K/mm^3
Hemoglobin (Hgb)	≥ 9.0 g/dL
Absolute Lymphocyte count	≥ 500/uL
Platelet Count	≥ 100,000/uL
Renal	
Calculated creatinine clearance	Serum Creatinine < 2.5 or ≥ 25 cc/min using a direct method or the Cockcroft-Gault formula
Urinary Protein Excretion	< 1.0 g/24 hours (as estimated by urine protein-creatinine ratio)
Hepatic	
Bilirubin	≤ 1.5 × upper limit of normal (ULN) (subjects with known Gilbert's disease who have serum bilirubin ≤ 3.0 x ULN may be enrolled)
Aspartate aminotransferase (AST)	≤ 2.5 × ULN (5.0 x ULN if Liver involvement)
Alanine aminotransferase (ALT)	≤ 2.5 × ULN (5.0 x ULN if Liver involvement)
Serum Albumin	≥ 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 × ULN (Note: This applies only to subjects who are not receiving therapeutic anticoagulation; subjects receiving therapeutic anticoagulation should be on a stable dose)

14. Females of childbearing potential must have a negative serum pregnancy test within 28 days prior to registration. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

15. Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 150 days (5 months) after discontinuation of atezolizumab and until 180 days (6 months) after discontinuation of bevacizumab. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:
    - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging
    - Hormone-replacement therapy or oral contraceptives

2. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to enrollment

3. Active or untreated CNS metastases or leptomeningeal disease as determined by CT or MRI evaluation during screening and prior radiographic assessments.

4. Subjects with treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:
    - Evaluable or measurable disease outside the CNS
    - No metastases to midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
    - No history of intracranial or spinal cord hemorrhage
    - No evidence of significant vasogenic edema
    - No ongoing requirement for dexamethasone as therapy for CNS disease; anticonvulsants at a stable dose allowed
    - No stereotactic radiation, whole-brain radiation within 4 weeks prior to Cycle 1 Day 1
    - Subjects with CNS metastases treated by neurosurgical resection or brain biopsy within 3 months prior to Cycle 1 Day 1 will be excluded.
    - Radiographic demonstration of interim stability (i.e., no progression) between the completion of CNS-directed therapy and the screening radiographic study
    - Screening CNS radiographic study ≥ 4 weeks since completion of radiotherapy or surgical resection and ≥ 2 weeks since discontinuation of corticosteroids

5. Uncontrolled tumor-related pain. **NOTE:** Subjects requiring pain medication must be on a stable regimen at study entry.

6. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

7. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. **NOTE:** Patients with asymptomatic hypercalcemia controlled with medical therapy are eligible.

8. Subjects who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

9. Subjects who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study.

10. Malignancies other than urothelial cancer within 5 years prior to Cycle 1 Day 1, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (T1/T2a, Gleason score $\leq 3 + 4$, and PSA ≤ 0.5 ng/mL undergoing active surveillance and treatment naive).

11. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study).

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

13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab or bevacizumab formulation.

14. 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 anti-phospholipid syndrome, granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
15. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.

16. Subjects with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.

17. Subjects with a history of celiac disease may be eligible if controlled with diet.

18. 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

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

20. History of confirmed positive test for HIV.

21. Subjects with active hepatitis B virus (HBV) (chronic or acute, defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C virus (HCV)

22. Subjects with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible.

23. Subjects positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

24. Active tuberculosis

25. 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

26. Signs or symptoms of active infection within 2 weeks prior to Cycle 1 Day 1

27. Received therapeutic oral or IV antibiotics within 1 week prior to Cycle 1 Day 1

28. Subjects receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.

29. Significant cardiovascular disease, such as:
    - New York Heart Association Congestive Heart Failure Class II or greater
    - Myocardial infarction, unstable angina or unstable arrhythmias within 3 months of enrollment.
    - History of stroke or TIA within 3 months of enrollment
    - Other clinically significant arterial vascular disease within 6 months of enrollment (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis). Prior history of adequately treated venous thromboembolism > 7 days prior to C1D1 on stable dose of therapeutic anticoagulation is permitted
    - Subjects 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.

30. 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 during the course of the study

31. Prior allogeneic stem cell or solid organ transplant

32. 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.

33. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the subject at high risk from treatment complications

3.3 Atezolizumab-Specific Exclusion Criteria

1. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies.

2. Prior cancer vaccines and cellular immunotherapy are permitted.

3. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, interleukin [IL]-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1 Day 1

4. 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

5. Subjects who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.

6. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency) is allowed.

3.4 Bevacizumab-Specific Exclusion Criteria

1. Inadequately controlled hypertension (defined as persistent systolic blood pressure (SBP) > 150 and/or diastolic blood pressure (DBP) > 100 mmHg)

2. Prior history of hypertensive crisis or hypertensive encephalopathy

3. Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)

4. Current or recent (within 10 days of study enrolment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), or current or recent (within 10 days prior to first dose of bevacizumab) use of therapeutic oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes. **NOTE:** The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the institution) and the subject has been on a stable dose of anticoagulants for at least two weeks at the time of study enrollment. Prophylactic use of anticoagulants is allowed.

5. History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month of study enrollment.

6. Minor surgical procedure within 7 calendar days prior to Cycle 1 Day 1

7. History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to enrollment

8. Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding

9. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure

10. Serious non-healing or dehiscing wound, active ulcer, or untreated or non-healing bone fracture

11. On-going gross hematuria associated with clots

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy. Subjects must begin therapy **within 3 business days** of registration.

5. TREATMENT PLAN

This is an open-label phase II study assessing the activity of bevacizumab combined with atezolizumab in metastatic urothelial carcinoma subjects who are ineligible for cisplatin-based therapy. Eligible subjects will be enrolled to receive treatment with:

- Atezolizumab 1200 mg IV flat dose *plus* Bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle. Subjects will be eligible to continue treatment until disease progression by RECIST v1.1 or unacceptable toxicity for up to 24 months.

5.1 Pre-medication and Hydration

There are no required pre-medications or intravenous hydration for treatment with atezolizumab in combination with bevacizumab. Institutional guidelines regarding pre-medication and hydration of atezolizumab and bevacizumab may be utilized.

5.2 Atezolizumab and Bevacizumab Administration

Table 3 Investigational Medicinal Product Dose and Administration

Drug	Dose	Route[2]	Schedule[3]	Cycle Length
Atezolizumab	1200 mg	Intravenously (IV)	Day 1	3 weeks (21 days)
Bevacizumab	15 mg/kg[1]	Intravenously (IV)[4]	Day 1	

[1] Bevacizumab dose will not be changed for reasons other than weight change of ≥ 10%.
[2] Please see section 6.2.1 and 6.2.2 for detailed guidelines re: drug administration
[3] Please see study calendar for schedule of treatments and evaluations.
[4] Bevacizumab should be administered a minimum of 5 minutes *after* atezolizumab

5.2.1 Atezolizumab Administration

Institutional guidelines with guidance from the investigator's brochure and/or package insert regarding all aspects of atezolizumab administration may be utilized including infusion times, windows for infusion times and treatment of infusion reactions. Administration of atezolizumab should be performed in a setting with emergency medical facilities available and staff who are trained to monitor for and respond to medical emergencies. The suggested infusion time for the initial dose of atezolizumab is 60 (± 15) minutes. Subsequent doses may be administered based on institutional guidelines. Subjects will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

5.2.2 Bevacizumab Administration

Institutional guidelines regarding all aspects of bevacizumab administration may be utilized including infusion times, windows for infusion times and treatment of infusion reactions. The suggested infusion time for the initial dose of bevacizumab is 90 (±15) minutes. Subsequent doses may be administered based on institutional guidelines. **Atezolizumab should be administered first** followed by bevacizumab, with a minimum of 5 minutes between dosing.

5.3 Concomitant Medications

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

5.3.1 Allowed Concomitant Medications

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

Subjects 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 β2-adrenergic agonists).

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the sponsor-investigator (unless exigent circumstances intervene). If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician after consultation with the sponsor-investigator.

The use of systemic or inhaled corticosteroids and/or mineralocorticoids (e.g., fludrocortisone) specifically for adrenal replacement in subjects with adrenocortical insufficiency or for treatment of orthostatic hypotension is allowed. Topical corticosteroids are also permitted. Megestrol administered as an appetite stimulant is acceptable while the subject is enrolled in the study.

Influenza vaccination should be given during influenza season only (approximately October to March). Subjects 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 vaccines.

Subjects who use hormonal therapy with gonadotropin-releasing hormone agonists or antagonists, oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low−molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use.

5.3.2 Prohibited Concomitant Medications

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.
    - After the completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if subjects are deriving benefit (e.g., treatment of known bony metastases, symptomatic hematuria).
    - Subjects experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment.
    - Subjects who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the sponsor-investigator.
- 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.

- Subjects who are receiving a receptor activator of nuclear factor kappa B (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 atezolizumab.
- Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is strongly discouraged.
- Subjects are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with Atezolizumab, could potentially increase the risk for autoimmune conditions.
- Subjects 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 Atezolizumab. Systemic corticosteroids and anti−TNF-α agents may attenuate potential beneficial immunologic effects of treatment with Atezolizumab but may be administered at the discretion of the treating physician after consultation with the sponsor-investigator. If feasible, alternatives to these agents should be considered.
- In addition, all subjects (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of Atezolizumab.
- Live vaccines within 4 weeks prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

5.4 Reproductive Information

Females of childbearing potential and males must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception from the time of informed consent until 150 days (5 months) after discontinuation of atezolizumab and until 180 days (6 months) after discontinuation of bevacizumab. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Atezolizumab Dose Delays/Modifications

There will be no dose reduction for atezolizumab in this study. Subjects may temporarily suspend study treatment if they experience toxicity that is considered related to a study drug and requires a dose to be held. If atezolizumab is held because of related adverse events for > 42 days beyond when the next dose would have been given, then the subject will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in the Study Calendar. If, in the judgment of the site investigator, the subject is likely to derive clinical benefit from resuming atezolizumab after a hold > 42 days, study drug may be restarted with the approval of the sponsor-investigator.

If subjects must be tapered off steroids used to treat adverse events, study treatment may be held for > 42 days. The acceptable length of interruption will depend on agreement between the site investigator and the sponsor-investigator.

If a known bevacizumab-related toxicity requiring temporary or permanent bevacizumab discontinuation develops, treatment with atezolizumab therapy may be continued at the treating physician's discretion. If a known atezolizumab-related toxicity requiring temporary or permanent atezolizumab discontinuation develops, treatment with bevacizumab therapy may not be continued.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with sponsor-investigator approval. The acceptable length of interruption will depend on agreement between the site investigator and the sponsor-investigator.

6.1.1 Management of Specific Adverse Events

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

6.1.1.1 Immune-Mediated Reactions

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids or other immunosuppressive agents.

The primary approach to Grade 1–2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune-mediated adverse events, atezolizumab should be withheld and oral/parenteral steroids administered. Recurrent Grade 2 immune-mediated adverse events may also mandate holding atezolizumab or the use of steroids. 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. Atezolizumab should be permanently discontinued in patients with life-threatening

immune-mediated adverse events. See the current Atezolizumab Investigator's Brochure and Appendix II for details on management of immune-mediated adverse events.

6.1.1.2 Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who develop a sepsis-like syndrome after administration of atezolizumab and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, review the atezolizumab investigator brochure for management guidelines and contact the sponsor-investigator for additional recommendations.

6.2 Bevacizumab Dose Modifications and Safety

If a known bevacizumab-related toxicity requiring temporary or permanent bevacizumab discontinuation develops, treatment with atezolizumab therapy may be continued at the treating physician's discretion. For equivocal cases, the treating investigator is advised to consult with the sponsor-investigator. If a known atezolizumab-related toxicity requiring temporary or permanent atezolizumab discontinuation develops, treatment with bevacizumab therapy may not be continued.

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

Concomitant medication use, AEs and SAEs will also be closely monitored throughout the study. All AEs will be graded according the NCI CTCAE v.4. Refer to the Bevacizumab Investigator's Brochure for a more details.

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for subjects on treatment with or without bevacizumab.

- Proteinuria will be monitored by urinalysis, urine dipstick, urine protein creatinine ratio, and/or 24 hour urine collection. (See Schedule of Events for detailed collection requirements.)
- If subjects on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Subjects undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that bevacizumab be restarted no earlier than 8 weeks after surgery).

Bevacizumab dose will not be changed (increase or decrease) for reasons other than a ≥10% change in weight from baseline. Bevacizumab treatment may be either temporarily or permanently suspended in the case of bevacizumab-related events such as fistulae, GI perforation, hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF, wound healing complications, PRES (or RPLS) and hypersensitivity/allergic reactions in addition to any other serious bevacizumab-related toxicity (grade 3 or 4). Guidelines for management of specific bevacizumab-related toxicities are outlined in the table below and the current package insert may be utilized for information:

Event	Action to Be Taken
Hypertension	
Grade 1 (asymptomatic, transient [< 24 hr] blood pressure increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	No bevacizumab dose modifications.
Grade 2 (recurrent or persistent [> 24 hr] or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	Withhold bevacizumab. Start antihypertensive therapy per institutional guidelines. After blood pressure is <150/100 mmHg, patient may continue bevacizumab.
Grade 3	Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 **(including hypertensive encephalopathy)**	Discontinue bevacizumab

Hemorrhage	
Grade 1 or 2 non-pulmonary or non-CNS events	No bevacizumab modifications.
Grade 3 non-pulmonary or non--brain or non-spinal cord hemorrhage	Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab.
Grade 4 non-pulmonary or non-brain or non-spinal cord hemorrhage	Discontinue bevacizumab.
Grade 1 pulmonary or brain or spinal cord hemorrhage	Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or brain or spinal cord hemorrhage	Discontinue bevacizumab
Venous thromboembolic event	
Grade 1 or 2	No bevacizumab modifications.
Grade 3 or asymptomatic **Grade 4**	If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic **Grade 4**	Discontinue bevacizumab.

Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive heart failure (left ventricular systolic dysfunction)	
Grade 1 or 2	No bevacizumab modifications.
Grade 3	Withhold bevacizumab until resolution to Grade 1.
Grade 4	Discontinue bevacizumab.
Urine Protein	
Urinalysis equivalent or urine dipstick ≤ 1+ protein AND/OR UPC ratio < 0.2 or 24 hour collection < 2g/24hrs	No bevacizumab modifications
Urinalysis equivalent or urine dipstick = 2+ protein	May administer bevacizumab and obtain urine protein creatinine ratio or 24 hour urine prior to next scheduled dose
Urinalysis equivalent or urine dipstick ≥ 3+ protein AND/OR UPC ratio ≥ 2 or 24 hour collection ≥ 2g/24 hrs	Hold bevacizumab and obtain urine protein creatinine ratio or 24 hour urine prior to next scheduled dose. Can resume bevacizumab when UPC ratio < 2 or 24 hour collection < 2g/24 hours
UPC ratio ≥ 3; nephrotic syndrome	Discontinue bevacizumab
GI perforation	
Any grade	Discontinue bevacizumab.
Fistula	
Any grade tracheoesophageal fistula	Discontinue bevacizumab.
Grade 4 fistula (other than tracheoesophageal)	Discontinue bevacizumab.
Bowel obstruction	
Grade 1	Continue patient on study for partial obstruction not requiring medical intervention.
Grade ≥ 2	Discontinue bevacizumab.
Wound dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.

Reversible posterior leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.
Fatigue/asthenia	
Grade 1 or 2	No bevacizumab modification
Grade 3	No bevacizumab modification
Grade 4	No bevacizumab modification
Event	**Action to Be Taken**
Hand-foot syndrome	
Grade 1 or 2	No bevacizumab modification.
Grade 3	Hold bevacizumab treatment; If it resolves to Grade ≤ 1 within 42 days, resume at - 1 dose level (if possible). If no resolution within 42 days, discontinue permanently.
Stomatitis	
Grade 1 or 2	No bevacizumab modification.
Grade 3	No bevacizumab modification.
Grade 4	No bevacizumab modification.
Hematologic toxicities (excluding anemia)	
Grade 1 or 2	No bevacizumab modification.
Grade 3 or 4	No bevacizumab modification.
Any grade Anemia	To be handled at the discretion of the investigator
GI = gastrointestinal; LMWH = low molecular-weight heparin; MRI = magnetic resonance imaging.[a]	

6.3 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined in section **Error! Reference source not found.**, a subject will also be discontinued from protocol therapy and followed up per protocol under the following circumstances:

- Evidence of disease progression per RECIST 1.1
- The site physician thinks a change of therapy would be in the best interest of the subject
- The subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
  - In case a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- A female subject becomes pregnant

- If protocol therapy is interrupted for > 42 days. Subjects who discontinued protocol therapy for reasons other than treatment-related grade 3 or 4 toxicity, may be considered for retreatment on study after consultation with the sponsor-investigator.

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

6.4 Protocol Discontinuation

If a subject decides to discontinue from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation 1 Cycle = approx 21 days	Screening		On Treatment	Safety follow up visits[13]	Long-term Follow up[14]
	-28 days of registration	-14 days of C1D1	Day 1 (± 3 days for Cycle ≥ 2)[15]	30 days post last dose ± 7 days	± 14 days
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History, Height, Diagnosis and Staging[1]	X				
Physical Exam[2]	X		X	X	
Vital Signs and ECOG Performance status[2]	X		X	X	
ECG	X				
AEs & Concomitant Medications		X	X	X	X
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff/plt (CBC)		X	X	X	
Comprehensive Metabolic Profile (CMP)[3]		X	X	X	
Uric Acid, Lactate Dehydrogenase[3]		X	X[3]	X	
PT/INR and aPTT		X			
Thyroid Function (TSH, Free T4, Free T3)[4]		X	X[4]		
Urinalysis or urine dipstick[5]		X	X[5]		
Pregnancy Test (serum or urine) for WOCBP[6]	X				
HBV and HCV Testing[7]	X				
DISEASE ASSESSMENT					
CT or MRI of chest[8]	X		X[8]	X	X
CT or MRI of abdomen and pelvis[8]	X		X[8]	X	X
CT of head or MRI Brain[8]	X				
Bone Scan[8]	X[8]		X[8]	X[8]	X[8]
TREATMENT EXPOSURE					
Atezolizumab 1200 mg IV			X		
Bevacizumab 15 mg/kg IV			X		

Study Evaluation 1 Cycle = approx 21 days	Screening		On Treatment	Safety follow up visit[13]	Long-term Follow up[14]
	-28 days of registration	-14 days of C1D1	Day 1 (± 3 days for Cycle ≥ 2)[15]	30 days post last dose ± 7 days	± 14 days
SPECIMEN COLLECTION					
Archival tumor tissue or screening biopsy[9]	X[9]				
On Treatment Biopsy[10]			X[10]		
Whole blood for germline testing[11]			X[11]		
Whole Blood for Biomarkers and cfDNA[11]			X[11]	X[11]	
Stool for microbiome analysis[12]			C1, C4[12]	X[12]	
FOLLOW UP					
Survival status					X
Subsequent therapy					X

Key to Footnotes

1: Medical History to include: Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging

2: Examinations performed as standard of care prior to obtaining informed consent but within 28 days of registration may be used rather than repeating tests. Vital signs to include temperature, heart rate, blood pressure, weight, and oxygen saturation and ECOG performance status.

3: CMP includes a basic metabolic panel (BMP) and liver function tests (LFTs). BMP will include sodium, potassium, chloride, CO2 (bicarbonate), calcium, creatinine, blood urea nitrogen and glucose; LFTs will include AST, ALT, total bilirubin, alkaline phosphatase, total protein and albumin. Uric Acid and Lactate dehydrogenase will be checked at screening, and at every other cycle beginning with Cycle 2.

4: Thyroid studies will be performed at screening before treatment initiation to include TSH, Free T4 and Free T3. TSH should be checked subsequently every 3 cycles on therapy.

5: Urinalysis (UA) and/or urine dipstick to estimate 24 hour urinary protein excretion is required at screening then prior to bevacizumab treatment on Day 1 of every cycle using an accepted conversion method as per institutional standard. Urine protein creatinine ratio or 24 hour urine should be collected for confirmation if UA or urine dipstick consistent with 2+ proteinuria or greater (see Section 6.2).

6: Urine or serum βhCG, within 28 days prior to Cycle 1 Day 1 of treatment and only if clinically appropriate (WOCBP). If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7: All subjects must undergo HBV and HCV testing. HBV testing includes hepatitis B core antibody [HBc Ab] and hepatitis B surface antigen [HBsAg]. HCV testing includes HCV antibody, and if positive, an HCV RNA polymerase chain reaction (PCR). HIV testing is optional and at the site investigator's discretion.

8: All measurable and evaluable lesions should be assessed and documented at screening. Tumor imaging will occur prior to the treatment Cycle that coincides with every 9 weeks for the first 12 months after C1D1 and then every 12 weeks thereafter while on study. Tumor response assessment will be performed by the site investigator and will consist of evaluation by CT or MRI of chest and MRI or CT of abdomen and pelvis. Imaging selected for each subject should remain the same throughout the study. Bone scan will be obtained at baseline if any clinical or laboratory suspicion of metastatic bone involvement. If bone scan is positive at baseline for metastases, it will be included with tumor response assessments

as noted above. CT of the head or MRI of brain should be performed at screening only to evaluate for the presence of brain metastases for all subjects. Tumor imaging may take place within 7 days prior to the study visit. Subjects who discontinue from treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments and document response in the eCRF until disease progression, withdrawal of consent, or death. Subjects who start a new anti-cancer therapy in the absence of disease progression should be followed according to the protocol schedule unless they withdraw consent. Site investigators may perform additional scans or more frequent assessments if clinically indicated.

9: Fixed paraffin-embedded blocks and/or 25 unstained slides will be requested for all subjects. Subjects with < 25 slides may be enrolled after discussion with the sponsor-investigator or co-investigator. Subjects who do not have archival specimen available must be willing to undergo tumor biopsy (core needle or excisional) during screening. The tumor tissue specimens for analysis may be from primary or metastatic tumor specimen. Subjects will be consented to optional storage of any remaining tumor samples after protocol-specified studies are complete. Stored samples will be reserved for future cancer-related research. Archival tissue or a fresh biopsy is required.

10: Subjects must be willing to undergo tumor biopsy on treatment, specifically between Cycle 1 and Cycle 2 of treatment if deemed safe and feasible by the site investigator. Subjects will be consented to optional storage of any remaining tumor samples after protocol-specified studies are complete. Stored samples will be reserved for future cancer-related research. See Correlative Laboratory Manual (CLM) for additional details. The on treatment biopsy is required.

11: Serial blood samples will be collected to support biomarker research (required). Whole blood will be collected for germline testing prior to treatment C1D1 only (required). Serum and plasma will be collected from a whole blood sample and peripheral blood mononuclear cells will be isolated per instructions in the CLM. Specific time points for collection prior to treatment: 1.) C1D1, 2.) C2D1 and 3.) Day 30 safety follow up visit. See CLM for additional details re: collection and storage.

12: Stool for microbiome analysis will be performed prior to treatment C1D1 and C4D1 (or safety visit whichever occurs first). Subjects will be provided a kit with detailed instructions regarding collection of the sample. The pre C1D1 sample may be collected any time after informed consent and prior to treatment C1D1. The pre C4D1 sample may be collected any time after completion of C3D1 treatment and prior to C4D1 treatment. Please see the CLM for additional details.

13: A safety follow-up visit should only occur when subjects permanently stop study therapy for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 (±7 days) after the last dose of therapy. Subjects who have an ongoing Grade ≥ 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved to baseline or deemed irreversible or clinically insignificant by the site investigator, or start of new therapy. If radiology imaging was done within 4 week prior to safety follow up visit it does not need to be repeated. If radiology imaging is needed it may be done -7 days prior to the safety visit.

14: Long-term follow up will occur every 3 months from the last dose of study therapy or until progression. Once disease progression is documented, subjects will enter a survival follow up period every 3 months for the first 2 years and then every 6 months thereafter up to 5 years from the time of treatment start. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

15: All labs (including urine) may be done up to 3 days prior to treatment. ± 3 days is to allow some flexibility with study drug administration but lab work will be obtained at least 72 hours prior to treatment with each cycle.

8. BIOSPECIMEN PROCEDURES AND CORRELATIVE STUDIES

8.1 Overview of Correlative Studies

Tissue and blood will be collected from all subjects enrolled in this study at time points described in the Study Calendar and CLM to test the following exploratory hypotheses. Additional investigational methods will be used to characterize and measure components of the immune response based upon the latest available technology at the time of analysis. If tissue or funds are limited, assay priority will be determined at the time of analysis.

Analysis of immune infiltrate will be performed using immunohistochemistry (IHC), immunofluorescence (IF), and computational approaches based upon RNA sequencing data. Immune regulatory molecules and populations of cells analyzed may include, but will not be limited to PD-L1, CD4, CD8, Tregs, B cells, macrophages, and dendritic cells and expression of biologically relevant/phenotypic markers thereof. We will perform high throughput DNA sequencing of the CDR3 region of the TCR beta chain in baseline tumors and pre- and post-treatment peripheral blood. We will perform a whole blood flow cytometry based assay to determine the MDSC and Treg percentage in pre- and post-treatment blood samples. We will analyze tumor associated myeloid cells and T regulatory cells in the tumor using IHC, IF, and computational approaches based upon RNA sequencing data. We will measure serum cytokines and proangiogenic proteins in the blood. We will conduct HLA typing, RNA expression profiling, and whole exome tumor/normal DNA sequencing of tumors, both at baseline and following therapy with bevacizumab and atezolizumab. Plasma cell-free (cf) DNA sequencing may also be used. Using neoepitope prediction tools commonly used in the field, we will quantify the number of predicted neoepitopes at baseline and assess the degree of change while on therapy. Next, we may identify candidate neoepitopes for further analysis, and assess for peripheral antigen-specific T-cell expansion/activation using intracellular cytokine or MHC tetramer loaded with the putative neoepitope flow cytometry staining. Tumor associated antigens, such as cancer germline antigens, may be evaluated using IHC, IF, or computational approaches based upon RNA sequencing.

8.2 Correlative Immune Hypothesis

8.2.1 Immune Hypothesis 1: Bevacizumab counteracts the immunosuppressive functions of VEGF and favorably alters the ratio of effector to suppressor immune cells, allowing for unopposed anti-PD-L1 mediated T-cell activation.

8.2.2 Immune Hypothesis 2

Bevacizumab induces cancer cell death, release of tumor-associated antigens (TAAs), dendritic cell maturation, antigen presentation, and activation of tumor-specific T-cell clones.

8.2.3 Immune Hypothesis 3

PD-L1 expression is dynamic, increases with inflammation, and may increase following therapy with bevacizumab. Thus, anti-PD-L1 may abrogate adaptive resistance.

8.2.4 Immune Hypothesis 4

There is a genetic basis for benefit from anti-PD-L1 blockade in bladder cancer.

8.3 Microbiome Analysis

- Collection of stool samples at baseline and on-treatment to perform metagenomic shotgun sequencing to characterize the microbial species present, targeted metabolomic assays, and bacterial culture. These analyses will power discoveries in:
  - Immune set point: Evaluating the impact of gut microbial heterogeneity on the development of T-cell driven anti-tumor immune responses.
  - Efficacy: Evaluating the gut composition of microbial species and metabolites present at baseline and their impact on response to therapy.
  - Safety: Evaluating how immunotherapy alters the gut microbiome and to test whether particular alterations contribute to the development of immune-related adverse side events (e.g. immune-related colitis).

8.4 Collection of Blood

Please refer to the Correlative Lab Manual (CLM) for additional information on collection, processing and shipping instructions.

Serum and plasma will be collected from whole blood and peripheral blood mononuclear cells will be isolated per instructions in the CLM. Specific time points for collection prior to treatment: 1.) C1D1, 2.) C2D1 and 3.) Day 30 safety follow up visit.

Biospecimens collected on this study will be used for the experiments/hypotheses described above, which are focused on determining mechanisms of response and resistance to immunotherapy with bevacizumab.

Excess biospecimens not completely utilized in these experiments will be stored indefinitely at HCRN for future use in experiments focused on bladder cancer that are yet to be determined. All specimens collected will maintain the assigned unique sequence ID of the corresponding patient. Deidentified samples may be shared with other research institutions. The linking key will remain with the site investigator at each participating institution. The storage of biospecimens for future cancer related research on this clinical trial is optional. We anticipate using most of the blood/biopsy samples before the study completion. We believe that allowing for storage and usage of the remaining samples for future cancer related research is ethically justified and a preferred option to discarding these materials given the potential impact on improving clinical outcomes for patients with bladder cancer. Patients will have the option to give permission for use of their samples in writing during informed consent. Patients may decide to withdraw their samples from storage or future use at any time after informed consent either verbally or in writing.

8.5 Collection of Tissue

See CLM for additional information regarding collection, processing and shipping instructions

8.5.1 Required Submission of Archival Tumor Tissue or Screening Biopsy

Archival Tissue

As indicated in the study calendar and in Section 8, fixed paraffin-embedded blocks and/or 25 unstained slides will be requested from tumor specimen in all subjects during screening.

Subjects with < 25 slides may be enrolled after discussion with the sponsor-investigator or co-principal investigator.

Screening Biopsy if Archival Tissue Not Available
Subjects who do not have archival specimen available must be willing to undergo tumor biopsy (core needle or excisional) during screening. The tumor tissue specimens for analysis may be from primary or metastatic tumor specimen.

Submission of Unstained Slides for Proposed Biomarker Evaluations
- Slides from FFPE-preserved archival tumor tissue or screening biopsy may be sent to Genentech or a Genentech designated 3rd party for staining of both baseline and post-treatment PD-L1 staining, to assess for baseline reactivity, induced PD-L1 expression, and correlation with the immune cell infiltrate.
- Slides from FFPE-preserved archival tumor tissue or screening biopsy will be sent to HCRN then shipped to MSKCC at a later date to undergo genomic analysis, immune expression profiling, and other interrogation to determine the mechanisms of response and resistance to therapy based on the latest available technology.

8.5.2 On Treatment Biopsy
All subjects must be willing to undergo tumor biopsy on treatment, specifically between Cycle 1 and Cycle 2 of treatment if deemed safe and feasible by the site investigator.

8.6 Stool Microbiome analysis
Stool for microbiome analysis will be performed prior to treatment C1D1 and C4D1 (or safety visit if the patient does not complete C4). Subjects will be provided a kit with detailed instructions regarding collection of the sample prior to the time point it is due. Please see the CLM for additional details.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease
Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded), as ≥10 mm with CT or MRI scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes
To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

9.8 Definitions for Response Evaluation – RECIST 1.1

First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR

Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

Duration of Response
Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

Objective Response Rate
The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

Disease Control Rate
The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

Time to Progression
A measurement from the date of registration until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

Progression Free Survival
A measurement from the date of registration until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be censored at the date of the last disease evaluation.

Overall Survival
Overall survival is defined by the date of treatment initiation to date of death from any cause. At the time of analysis, if a subject has not died, the subject will be censored on the date of last follow-up.

10. STUDY DRUG INFORMATION
Refer to Investigator's Brochure (IB) and/or prescribing information for detailed information on toxicity associated with each drug.

10.1 Bevacizumab

10.1.1 Supplier/How Supplied
Bevacizumab is supplied by Roche/Genentech as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400-mg (25 mg/mL) glass vial contains 16 mL of bevacizumab (25 mg/mL) with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP. Vials contain no preservative and are for single use only. For further details, please see the bevacizumab investigator's brochure.

10.1.2 Dosage, Formulation and Administration
Subjects will receive bevacizumab 15 mg/kg by intravenous infusion according to product label once every 21 days. The bevacizumab dose will be based on the subject's weight at baseline (cycle 1, day 1) and will remain the same throughout treatment on protocol unless there is a change in weight of ≥ 10%.

Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

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

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

10.1.3 Storage and Stability

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Keep vial in the outer carton due to light sensitivity.

VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C–30°C in 0.9% Sodium Chloride solution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

10.2 Atezolizumab

10.2.1 Supplier/How Supplied

Atezolizumab will be supplied by the Roche/Genentech. 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.

10.2.2 Dosage, Formulation and Administration

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion every 21 days. No dilution of the vial contents is required.

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 MPDL3280A in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

For further details regarding drug preparation, storage, and administration, see the atezolizumab IB.

Any overdose or incorrect administration of study drug should be noted on the electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

10.2.3 Storage and Stability

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.

10.2.4 Investigational Medicinal Product Accountability and Disposal

All investigational medicinal products (IMPs) required for the completion of this study (atezolizumab and bevacizumab) will be provided by the drug manufacturer (Roche/Genentech) via a third party distributer. The investigational site will acknowledge receipt of atezolizumab and bevacizumab and confirm shipment content and condition. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned with the appropriate documentation. The site's method of IMP destruction must be agreed upon by HCRN. The site must obtain written authorization from HCRN before any IMP is destroyed and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to and disposed of by the study site should be recorded on the Drug Inventory Log.

10.2.5 Dispensing

Both investigational products used in this study will be provided by the drug manufacturer. Atezolizumab and bevacizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Atezolizumab and bevacizumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.3 Adverse Events of Bevacizumab and Atezolizumab

Please refer to the Investigator Brochures for atezolizumab and bevacizumab for a detailed summary of adverse events previously reported with these agents.

11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any unfavorable and unintended medical occurrence during the course of the study whether or not considered related to the study therapy. The following are examples of AEs:

- A sign (including an abnormal laboratory finding) or symptom
- A disease temporally associated with participation in an investigational study
- An intercurrent illness or injury that impairs the well-being of the subject
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with urothelial carcinoma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- 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.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the site investigator to the study therapy.

11.1.2 Adverse Events of Special Interest for Bevacizumab and Atezolizumab

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

AEs of Special Interest (AESI) for *bevacizumab* are defined as:

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

AEs of special interest for *Atezolizumab* include the following:

- Pneumonitis
- Colitis
- Endocrinopathies: Diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism and hypophysitis

- Hepatitis including AST/ALT > 10x ULN
- Systemic Lupus Erythematosus
- Neurological disorders: Guillian-Barre Syndrome, Myasthenia Gravis, or myasthenic syndrome, and Meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release syndrome, influenza like illness, macrophage activating syndrome and hemophagocytic lymphohistiocytosis
- Ocular toxicities (uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade > 2 cardiac disorders (e.g. atrial fibrillation, myocarditis, and pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g. Stevens-Johnson Syndrome, dermatitis bullous, toxic epidermal necrolysis)

11.1.3 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. NOTE: Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.4 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.5 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***clearly not related*** to the drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

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

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

No
Evidence exists that the AE has an etiology other than the atezolizumab and/or bevacizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab and/or bevacizumab 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.

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of informed consent until 30 days after treatment discontinuation.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

11.2.2 Site Requirements for Reporting SAEs and AEs of Special Interest (AESI) to HCRN

- SAEs caused by a protocol-mandated intervention occurring after informed consent but prior to initiation of study therapy will be reported (e.g. SAEs related to invasive procedures such as biopsies or medication washout).

- SAEs related and unrelated to the study therapy and AESIs that occur on or after initiation of study therapy until 30 days after last dose of study therapy will be reported **within 1 business day** of discovery of the event.
- All SAEs and AESIs will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs occurring after discontinuation of study drugs if attributed to prior atezolizumab or bevacizumab exposure.
- For any pregnancy in a female subject or a female partner of a male subject while receiving the study drug or within 5 months after the last dose of atezolizumab or within 6 months after the last dose of bevacizumab, the site investigator will report the pregnancy **within 1 business day** of discovery and follow the female subject until completion of the pregnancy. Outcome of the pregnancy (either normal or abnormal outcome) must be documented in the medical record and a Pregnancy Form completed. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the site investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria as outlined above, it must be reported as an SAE.

The completed SAE Submission Form must be sent to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Follow-up information should be submitted to HCRN electronically to safety@hoosiercancer.org using a SAE Submission Form stating that this is a follow-up to the previously reported SAE and providing the follow-up number if appropriate. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the subject continued or withdrew from study participation.

11.2.3 HCRN Requirements for Reporting SAEs, Pregnancy and AESIs to Roche/Genentech

HCRN will report ALL SAEs, Pregnancies, and AESIs, special situation reports and product complaints (with or without AE) that occur after the subject has been exposed to the study drug, to Roche/Genentech **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Roche/Genentech as it is received from site.

Single Case Reports To Genentech/Roche:
Central Operations Mailbox: usds_aereporting-d@gene.com
Fax: 650-238-6067

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 HCRN Responsibilities to FDA

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the Roche/Genentech's parent IND at the time of submission. Additionally, HCRN will submit a copy of the annual FDA safety report to Roche/Genentech as soon as reasonably possible after completion.

11.5 IND Safety Reports Unrelated to this Trial

Genentech/Roche will provide HCRN with any IND safety reports from external studies that involve the study drug(s) per their guidelines. IND safety reports should be sent electronically to safety@hoosiercancer.org. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent.

HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Study Design

In July 2018, this study was modified from its original design of a randomized study of atezolizumab with or without bevacizumab to the current single arm design of atezolizumab in combination with bevacizumab. The study was amended due to a safety alert issued by the FDA in May 2018 identifying shorter survival for PD-L1 low/negative patients with advanced urothelial cancer treated with first line atezolizumab compared to platinum-based chemotherapy in a separate phase III trial (IMVigor 130). In July 2018, the FDA issued a change in the prescriber label for atezolizumab, limiting use in first-line cisplatin-ineligible advanced urothelial cancer to PD-L1 positive patients or to those who are ineligible for any chemotherapy.

Given concerns for shorter survival for single agent use in PD-L1 low/negative patients in this population, the study was modified to a single arm design of atezolizumab combined with bevacizumab. Subjects enrolled into this study will be treated with atezolizumab 1200 mg IV and bevacizumab 15 mg/kg IV on day 1 of an every 21 day cycle until unacceptable toxicity or RECIST v1.1 defined disease progression.

12.2 Objectives

12.2.1 Primary Objective

- Overall survival (OS) rate will be assessed at 1 year.

12.2.2 Secondary Objectives

- Objective Response Rate (ORR) (defined in section 9)
- Duration of Response (DoR) (defined in section 9)
- Disease Control Rate (ORR + SD) (defined in section 9)
- Progression-Free Survival (PFS) (defined in section 9)
- Safety and Toxicity by CTCAE v4

12.3 Sample Size and Accrual

This is a single arm clinical trial with 1 year OS (overall survival) as a binary endpoint. We assume 57% 1 year OS null rate based on OS observed in a phase II trial of atezolizumab as first-line therapy in cisplatin-ineligible metastatic urothelial cancer patients (IMvigor 210 Cohort 1)[54] and 72% as desirable 1 year OS rate. We will accrue 70 patients to treatment with atezolizumab and bevacizumab on this study. If 46 patients or more are alive at 1 year, the treatment will be deemed promising. This design has 10% one-sided type 1 error and 90% power.

12.4 Assessment of Safety

All subjects enrolled and who receive at least 1 dose of study treatment will be followed for safety and toxicity. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)) v4 will be used to assess and monitor safety on this study. Please see the Study Calendar in section 8.0 for the schedule of safety/toxicity assessment.

12.5 Assessment of Efficacy

All subjects enrolled to this study, regardless of whether study treatment is received will be followed for the primary endpoint of survival and secondary endpoints with an intent-to-treat analysis.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

The study will accrue 70 patients to atezolizumab and bevacizumab therapy and the primary endpoint will be 1 year overall survival, where 57% 1 year OS is considered the null rate, and 72% 1 year OS as desirable rate considered promising for further study. If 46 or more patients are alive at 1 year, the study will have met its primary endpoint and the treatment will be deemed promising. This design has 10% type 1 error and 90% power.

The primary endpoint will be analyzed as a binary endpoint when all alive patients have at least 1 year of follow-up.

As a secondary analysis overall survival will be analyzed as a time to event endpoint using the Kaplan Meier method. Overall survival will be defined as the time from treatment initiation until

death by any cause. At the time of analysis, if a subject has not died, the subject will be censored on the date of last follow-up.

12.6.2 Analysis Plans for Secondary Objectives

Objective Response Rate (ORR)
Objective response rate is defined as the proportion of subjects achieving either partial response or complete response by RECIST v1.1.

ORR will be reported as an estimate using binomial proportions with 95% confidence intervals.

Duration of Response (DoR)
Duration of response is defined as the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started) by RECIST v1.1.

DoR will be reported as an estimate of the median with range.

Disease Control Rate (ORR + SD) for both treatment arms
The disease control rate is the proportion of all subjects with stable disease (SD) or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

Disease control rate will be reported as an estimate using binomial proportions with 95% confidence intervals.

Progression-Free Survival (PFS)
Progression-Free survival will be defined as the time from the date of registration until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed nor died at the time of last follow up will be censored at the date of the last disease evaluation.

PFS will be analyzed using the Kaplan Meier method and reported as an estimate of the median and rate at 1 year with 95% confidence intervals.

Safety and Toxicity by CTCAE v4
Safety and toxicity will be compiled and reported in tabular format by the nature, frequency and severity of toxicities as well as relationship to study treatment.

12.6.3 Analysis Plans for Exploratory Objectives
Listed in Section 8.2 and 8.3 respectively are immune related hypotheses for tissue/blood and microbiome analyses and the plan for exploratory analyses. For tissue/blood-based analysis, additional or different investigational methods will be used to characterize and measure components of the immune response based upon the latest available technology at the time of

analysis. Left-over specimens may be stored for future cancer related studies. If tissue availability or funding is limited, assay priority will be determined at the investigators discretion.

The exploratory hypotheses listed in section 8.2 are hypothesis generating. As such, all four of the exploratory analyses will be descriptive and graphical in nature. To test the associations between clinical outcomes and biomarkers we will use Fisher's exact or Wilcoxon rank sum tests for binary or continuous variables, respectively.

For exploratory associations between microbiome composition and outcomes to immunotherapy treatment on this study, stool samples will be collected at baseline and on-treatment to perform metagenomic shotgun sequencing to characterize the microbial species present, targeted metabolomic assays, and bacterial culture. These analyses will power discoveries evaluating the impact of the microbiome on the host immune set point, treatment efficacy and treatment safety. As these analyses are exploratory in nature, descriptive statistics will be used.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2011 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULMC PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by DSMC semi-annually (from the date the first patient is enrolled) and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Additional reviews may be scheduled based on SAE reports, investigator identified issues, external information, etc.

HCRN oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator (Arjun Balar MD) and NYU Perlmutter Cancer Center DSMC

Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

13.1.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan detailed below. The site investigator will allocate adequate time for such monitoring activities. The site investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. At each visit, the monitor will review various aspects of the trial including, but not limited to: compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause audits may be performed as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

During scheduled monitoring visits, the site investigator and the investigational site staff must be available in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the HCRN study team and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The site investigator must promptly inform HCRN of any audit requests by health authorities, and HCRN will provide Roche/Genentech with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

13.2 Data Quality Oversight Activities

Remote validation of EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

The trial site may also be subject to quality assurance audit by Genentech or its designee as well as inspection by appropriate regulatory agencies.

13.3 Amendments

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol (amended protocol) and/or the revised informed consent will be generated by HCRN and must be approved by the sponsor-investigator, Genentech/Roche (if required by the contract), the FDA (if applicable), and each site's IRB.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform, a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and HCRN.

14.2.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source

data are contained in source documents. Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into the EDC system. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. All study personnel have passed human subject protection courses. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Samples that are collected will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Genentech/Roche, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15. ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to

recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

Consent will be obtained only by a site investigator who has completed requisite training for human subject research. The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. The patient should be given the opportunity to ask questions and allowed time to consider the information provided. Questions will be answered by a site investigator, or qualified research study team member all of whom have completed requisite training for human subject research. Site investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Site investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

This informed consent should be given by means of standard written statement, written in non-technical language. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval.

All patients will be required to sign a written informed consent prior to being registered on this study. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

15.3.1 Documentation of Consent

The sponsor-investigator or IRB approved site investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant and the original signed consent forms will be stored in the subject's chart.

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17. APPENDIX I

Appendix 1: ECOG Performance Status

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology

APPENDIX II: MANAGEMENT OF ATEZOLIZUMAB-SPECIFIC ADVERSE EVENTS

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

PULMONARY EVENTS

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

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

Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as a Grade 3 or 4 event
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab. [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.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

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

HEPATIC EVENTS

Immune-related hepatitis has been associated with the administration of atezolizumab.–Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

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

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

Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue 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 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 atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 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.

LFT = liver function tests.

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

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

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

GASTROINTESTINAL EVENTS

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

Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [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 atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI 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 atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI 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.

GI = gastrointestinal.

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

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

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

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

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

Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. c
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 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

Event	Management
	on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold 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. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab [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. • Initiate hormone replacement if clinically indicated.

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

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).

Management Guidelines for Ocular Events

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

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

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

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

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy. All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated. Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines 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 atezolizumab for up to 12 weeks after event onset [a] • 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 atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab. [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.

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

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

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

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction [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.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or**	• Immediately interrupt atezolizumab 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

Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3[a] Fever[b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab.[f] • 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. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • 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.
Grade 4[a] Fever b with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab.[f] • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[g] may be considered at the discretion of the investigator. • Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
b. Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
d. Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate). 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 considering the benefit-risk ratio.
g. Refer to Riegler et al. [32] for information on experimental treatments for CRS.

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 1	• Continue atezolizumab • Monitor amylase and lipase prior to dosing
Amylase and/or lipase elevation, Grade 2	• Continue 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 atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI 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 atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI 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.

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

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

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

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. 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

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • 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, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only

after approval has been documented by the investigator (or an appropriate delegate).

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies.

Management Guidelines for Neurologic Disorders

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

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

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

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

IMMUNE-RELATED MENINGOENCEPHALITIS

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

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines below.

Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. [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.

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

IMMUNE-RELATED NEPHRITIS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal 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 atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. a • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. b • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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.

a. Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the sponsor-investigator.
b. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor-investigator.

IMMUNE-RELATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatinine-kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle-biopsy. One etiology of myositis is immune-mediated, which is the current concern with atezolizumab.

It is recommended that atezolizumab should be withheld for moderate or severe (Grade 2 or 3) immune-related myositis and permanently discontinued for recurrent severe or life-threatening myositis (recurrent Grade 3 and Grade 4). Please refer the patient to rheumatologist and/or neurologist and consider muscle biopsy and supportive measures as clinically indicated. Corticosteroids treatment with 1-2 mg/kg/day IV methylprednisolone or higher-dose bolus if severely compromised (weakness severely limiting mobility, cardiac function, respiratory function, dysphagia) and/or additional immunosuppressive agents should be administered for ≥ Grade 2 events or if the event does not improve after initial corticosteroids. Please refer to the table below for detailed management guidelines for immune-mediated myositis.

Management Guidelines for Immune-Related Myositis

Event	Management
Immune-related myositis, Grade 1	• Continue atezolizumab • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines
Immune-related myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact site investigator. • Refer subject to rheumatologist or neurologist • Initiate treatment as per institutional guidelines • Consider treatment with corticosteroid equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor-investigator. [c]
Immune-related myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset[a] and contact site investigator.

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

IV, intravenous

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

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in subjects who are deriving benefit and have fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the sponsor-investigator.