SUMMARY OF CHANGES – Protocol

For Protocol Amendment: A Phase 2 Study of Atezolizumab (MPDL3280A) in Combination with Bevacizumab in Patients with Recurrent, Persistent or Metastatic Cervical Cancer

NCI Protocol #:10010

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#	Section/ Page	Comments
1	N/A	The protocol version date was updated to 02/06/2018 throughout the protocol.
2	N/A	Formatting and editorial changes were made throughout the protocol.
3	Title Page	Stella Krawiec added as LAO Protocol Liaison.
4	9.1.1.2	Pre-treatment/biopsy sample shipping address updated.
5	Study Calendar	Treatment window revised.
6	Table of Contents	Table of Contents page numbers revised.
7	1.2.2 7.2 7.3.3 13.1 13.4	CTCAE version changed from 4.0 to 5.0 throughout the protocol to reflect CTEP updated amendment request dated 01/25/2018.

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TITLE: A Phase 2 Study of Atezolizumab (MPDL3280A) in Combination with Bevacizumab in Patients with Recurrent, Persistent or Metastatic Cervical Cancer

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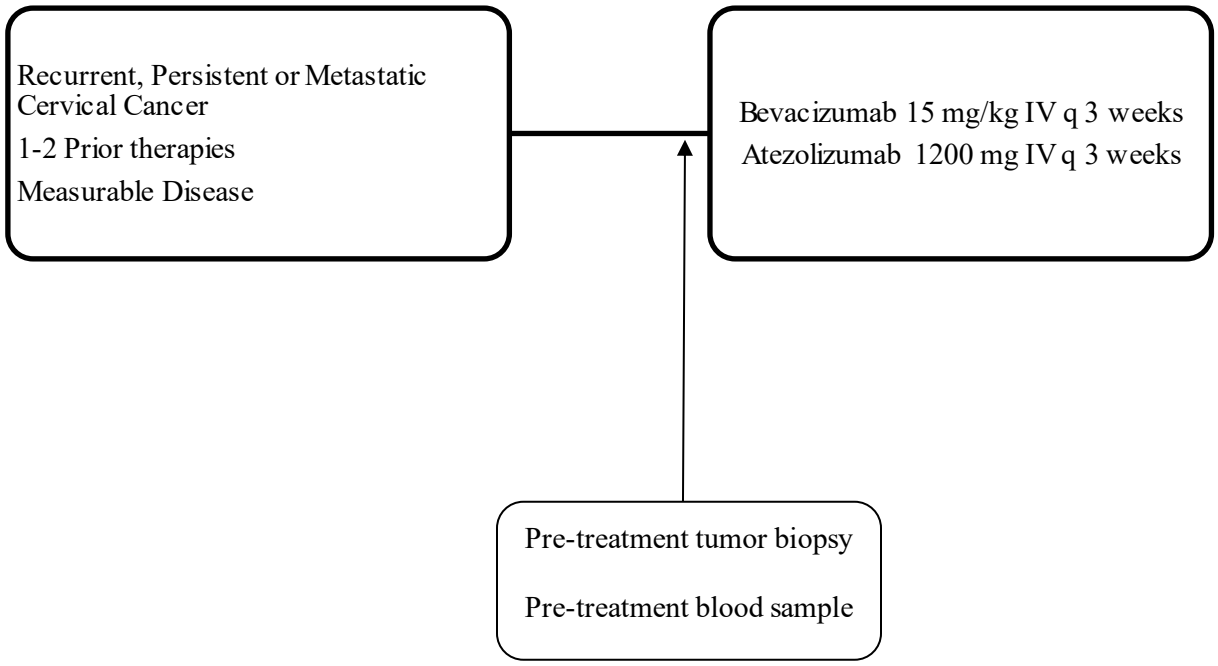
STUDY SCHEMA

This is a Phase II, multi-institution study entitled, "Phase II study of Atezolizumab and Bevacizumab in Patients with Recurrent, Persistent or Metastatic Cervical Cancer." In this study, patients with recurrent, persistent or metastatic cervical cancer who have received one to two prior therapies in the recurrent, persistent or metastatic disease setting will be treated with the combination of bevacizumab 15mg/kg intravenous (IV) every 3 weeks and atezolizumab 1200mg IV every 3 weeks until progression of disease (POD), unacceptable toxicity or withdrawal from study. All treatments will be administered in the outpatient setting. The primary objective is to measure the objective response rate (ORR, either partial or complete response) defined by RECIST v1.1 criteria. Secondary endpoints include progression-free survival (PFS), overall survival (OS) and safety.



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1. OBJECTIVES

1.1 Primary Objectives

To assess the anti-tumor activity (proportion of patients with objective response by RECIST 1.1 criteria) of atezolizumab and bevacizumab in patients with recurrent, persistent or metastatic cervical cancer.

1.2 Secondary Objectives

1.2.1 To estimate the duration of progression free survival (PFS) and overall survival (OS)

1.2.2 To assess safety by CTCAE v.5.0

1.2.3 Integrated Biomarker: To describe the efficacy of the combination of atezolizumab and bevacizumab as measured by objective response, by PD-L1 expression on tumor and immune cells measured by semi-quantitative immunohistochemistry (IHC)

1.2.4 Exploratory Biomarker: To describe the efficacy of the combination of atezolizumab and bevacizumab as measured by objective response, by intratumoral and peripheral TCR clonality and tumor infiltrating lymphocyte proportion

2. BACKGROUND

2.1 Study Disease(s)

2.1.1 Cervical Cancer

In the United States, it is estimated that 12,990 women will be diagnosed with cervical cancer and 4,120 women will die of the disease in 2016 (http://www.ncbi.nlm.nih.gov/pubmed/26742998). Worldwide, cervical cancer is the fourth most common cancer and the most common cause of mortality in women, with 528,000 new cases and an estimated 266,000 deaths in 2012 (http://www.ncbi.nlm.nih.gov/pubmed/25220842).

The human papilloma virus (HPV) is recognized to be the primary etiologic agent for cervical carcinogenesis. However, the majority of HPV-infected individuals have an asymptomatic course, with clearance of the virus occurring within 1 or 2 years in 90% of cases. Ten percent of individuals experience persistent HPV infection, which increases their risk of developing invasive cancers. Ultimately, approximately one half of the 10% of individuals with persistent HPV infection will develop malignant disease, a process that may take up to 30 years (http://www.ncbi.nlm.nih.gov/pubmed/21282563). Although many HPV types have been associated with cervical neoplasia, types 16, 18, 31, 35, 39, 45, 51, 52, 56, and 58 cause most invasive cancers and are considered "high-risk" HPV-genotypes. HPV-16 accounts for approximately 53% of invasive cervical cancer cases in most countries, followed by HPV-18, which accounts for approximately 13% (http://www.ncbi.nlm.nih.gov/pubmed/19318628). The high-risk HPV genotypes

produce 2 oncoproteins, designated E6 and E7, which bind and inactivate the tumor suppressor's p53 and retinoblastoma protein (pRB), respectively. The E6 mediated inhibition of p53 blocks apoptosis, whereas E7 inhibition of pRB abrogates cell cycle arrest leading to dysregulated cellular proliferation and ultimately malignancy (http://www.ncbi.nlm.nih.gov/pubmed/12502868).

Outcomes for patients with recurrent, persistent or metastatic cervical cancer are poor. First-line therapy with bevacizumab in combination with paclitaxel/cisplatin or paclitaxel/topotecan is been approved by the Food and Drug Administration (FDA) based on GOG 240 (http://www.ncbi.nlm.nih.gov/pubmed/24552320). Treatment with this combination increased overall survival from 13.3 to 17 months, (HR 0.71 [98% CI, 0.54-0.95; p=0.004]), and the ORR increased from 36 to 48% (p=0.008) when compared to chemotherapy without bevacizumab. Seventy-five percent of patients entering GOG240 had prior concurrent chemotherapy and radiation therapy (CCRT) with cisplatin. The remaining 25% were treatment naïve. Following this first line treatment with chemotherapy with or without bevacizumab, there is no usual care second line therapy with significant activity. In GOG 227C, a phase II study of single agent bevacizumab (in patients without prior bevacizumab), treatment was shown to be well-tolerated and active in the second and third-line treatment of patients with recurrent cervical cancer (23.9% PFS at 6 months and 10.9% response rate, n=46 patients) (http://www.ncbi.nlm.nih.gov/pubmed/19139430).

2.1.2 **Cervical Cancer and Immunotherapy**

Cervical cancers have a lower median mutational burden than other checkpoint-blockade sensitive malignancies (range of approximately 1-10 mutations per megabase, as compared to 1 to 100 in melanoma, (http://www.ncbi.nlm.nih.gov/pubmed/23945592). To increase the proportion of benefiting patients, cervical cancer must be made "visible" to the immune system, which may require targeting of disease specific immune targets and/or target enhancement through judicious combinations. Strategies to improve activity of PD-L1/PD-1 blockade include immune combinations (e.g., CTLA4/ipilimumab), chemotherapy combinations and targeted therapy combinations (e.g., anti-vascular).

Results to date show modest activity for **single agent** anti-PD-1 and anti-CTLA4 therapies. A study of single agent anti-PD-1 treatment with nivolumab in recurrent, persistent or metastatic cervix cancer has completed accrual and is in follow-up (NRG GY002, NCT02257528), n=26 patients. A phase I/II study of ipilimumab in metastatic or recurrent cervical carcinoma has completed accrual. Preliminary results of 42 enrolled patients, presented at ASCO 2015, showed one confirmed partial response (J Clin Oncol 33, 2015 (suppl; abstr 3061)). Cervical squamous cell cancer is under evaluation in the Phase Ib KEYNOTE-028 study (pembrolizumab). Preliminary results presented at ASCO 2016 show ORR of 12.5% (3/24) (J Clin Oncol 34, 2016 (suppl; abstr 5515)). Further evaluation of pembrolizumab is planned in the KEYNOTE-158 study (NCT02628067).

Evaluation of combinations holds promise. A study of nivolumab and nivolumab plus ipilimumab in viral-associated tumors (NCT02488759) is ongoing. SWOG is planning a trial of nivolumab and ipilimumab in treating patients with rare tumors (NCT02834013),

that will include cervical cancer, vaginal cancer and vulvar cancer cohorts.

2.1.3 Rationale for Atezolizumab in Advanced Cervix Cancers

Given the parallels in disease pathogenesis and treatment between HPV associated cervix and head and neck cancers (HNSCC), their comparison may be informative. Promising data from HNSCC suggest that checkpoint blockade therapies may be effective in cervical cancer.

PD-L1 has been found to be upregulated in cervical intraepithelial neoplasias (CINs) (20/21 cases) and cervical squamous cell cancers (56/70) relative to normal cervical epithelia (0/55) (http://www.ncbi.nlm.nih.gov/pubmed/26403783). While one study found PD-L1 expression to be associated with HPV positivity (http://www.ncbi.nlm.nih.gov/pubmed/23521696), in another (http://www.ncbi.nlm.nih.gov/pubmed/19825956), PD-L1 was only expressed in 19% of cervical carcinomas; however, a tissue microarray was used for this study which may underestimate PD-L1 prevalence in a given sample. PD-L1 expression does not appear to be different between HPV (+) and (-) oropharyngeal squamous cell cancers (http://www.ncbi.nlm.nih.gov/pubmed/26511814). Nonetheless, the success of TIL therapy in a small study of HPV (+) patients (ORR 3/9 with 2 CRs, http://www.ncbi.nlm.nih.gov/pubmed/25823737) suggests that there is potential for an effective anti-tumor T cell response in this disease.

In terms of the clinical significance of HPV positivity, in HNSCC, a history of infection may impact long term outcome but not response rate to checkpoint blockade. This could be, in part, due to the fact that most HPV (-) HNSCC are associated with cigarette exposure, and thus tumors are likely to have a higher mutational burden. In a Phase IB study of pembrolizumab at 10mg/kg q2 weeks in patients with HNSCC, the ORR was 20% overall and 50% in the 12 patients with high PD-L1 expression (Chow LQ et al Ann Oncol 25(suppl 4):S1–S41). The ORR was 4/23 (20%) in the HPV (+) patients, and 7/38 (19%) in HPV (-). However, the PFS and OS were longer in HPV positive patients: PFS (95% CI) of 17.1 (8-41.7) vs 8.1 (7.9-15.6) weeks in HPV (+) versus HPV (-), and OS of not reached (9.6-NR) vs. 9.5 (3.9-12.6) weeks in HPV (+) versus HPV (-), respectively. While it is not possible to ascertain whether the drug or inherent disease behavior was responsible for this difference, it is nonetheless promising that those patients with HPV+ disease fared better.

In a study of pembrolizumab in HNSCC, of 99 evaluable patients, the RR was 24.8% with an additional 24.8% of patients having stable disease, yielding a DCR of 49.6% (Seiwart et al J Clin Oncol Vol 33, 2015). In that study, the response rate was slightly lower in HPV (+) patients (20.6%, 95% CI 8.7-37.9) compared to HPV (-) (27.2%, 95% CI 17.9-38.2). This study did not report PFS/OS in HPV (+) versus negative patients. In another study of MEDI4736 in 62 patients with HNSCC, the ORR was 11% (18% in PD-L1 positive tumors; 8% in PD-L1 negative tumors) (Segal et al J Clin Oncol 33, 2015), and was not different between HPV (+) and (-) patients.

2.2 CTEP IND Agent

2.2.1 **Atezolizumab (MPDL3280A)**

Atezolizumab (MPDL3280A) is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells (Investigator's Brochure, 2015). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

2.2.1.1 Mechanism of Action

PD-L1 expression is prevalent in many human tumors (*e.g.*, lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (Thompson *et al.*, 2006; Hamanashi *et al.*, 2007; Okazaki and Honjo 2007; Hino *et al.*, 2010). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1), and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer (Blank *et al.*, 2005; Keir *et al.*, 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen, 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Unlike PD-L1, programmed death-ligand 2 (PD-L2) is primarily expressed in normal tissues such as the lung. As a result, targeting tumor-overexpressed PD-L1 is a more promising strategy than targeting PD-1, as it preserves the immune homeostatic PD-L2:PD-1 interaction in normal tissues while dually inhibiting the PD-L1:PD-1 and PD-L1:B7.1 pathways to enhance anti-tumor T cell immunity.

Blockade of PD-L1 or PD-1 with monoclonal antibodies has been reported to result in strong and often rapid antitumor effects in several mouse tumor models (Iwai *et al.*, 2002; Strome *et al.*, 2003). These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or inhibited state, and blockade of the PD-L1/PD-1 pathway can reinvigorate tumor-specific T-cell responses.

Collectively, these data establish the PD-L1/PD-1 pathway as a promising new therapeutic target in patients with advanced tumors. Immune-related adverse events

(AEs) reported from the two recent studies were consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance.

2.2.1.2 Summary of Nonclinical Experience

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

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

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

2.2.1.3 Summary of Clinical Experience

Current clinical studies of atezolizumab include one ongoing phase 1a monotherapy study, three ongoing combination studies, five phase 2 studies, and one phase 3 study. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

2.2.1.3.1. Clinical PK and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab shows linear PK at doses ≥1 mg/kg (Investigator's Brochure, 2015). At doses ≥1 mg/kg, the mean maximum plasma concentration (C_{max}) increased in a dose-proportional manner and was 26.0 mcg/mL for the 1 mg/kg dose group and 472 mcg/mL for the 20 mg/kg dose group. Similarly, at doses ≥1 mg/kg, the group mean area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$) had a range of 340 to 6050 day × mcg/mL and was approximately dose proportional, as evidenced by similar clearance (CL) across the dose range. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent CL and the mean steady-state volume of distribution (V_{ss}) had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg) (Investigator's Brochure, 2015). Patients dosed at the 10-, 15-, and 20-mg/kg dose levels maintained the expected target trough levels of drug despite the detection of ATAs. Accordingly, the development of detectable ATAs does not appear to have a clinically significant impact on PK for doses from 10 to 20 mg/kg. To date, no relationship between the development of measurable ATAs and safety or

efficacy has been observed.

2.2.1.3.2. Clinical Safety Summary

As of 10 May 2016, an estimated total of 6053 patients with solid tumor and hematologic malignancies have received atezolizumab in clinical trial participation as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy.

Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been determined. Across all studies and tumor types, the most commonly reported adverse events with single-agent atezolizumab include fatigue, nausea, decreased appetite, diarrhea, constipation, and cough.

The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each study treatment. Systemic immune activation, characterized by an excessive immune response, is a potential risk associated with atezolizumab when used in combination with another immunomodulating compound.

The percentage of patients who discontinued atezolizumab due to any adverse event is consistent when used as a single agent or in combination with chemotherapy (e.g., 5.4% in Study PCD4989g and 5.8% in Study GP28328, respectively). The percentage of patients with any Grade 5 adverse event was similar when used as a single agent or in combination with chemotherapy (e.g., 1.6% in Study PCD4989g and 1.0% in Study GP28328).

Immune-related adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-related adverse events are closely monitored during the atezolizumab clinical program. To date immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis. Immune-related adverse events and guidance regarding the management of immune-related adverse events are provided below:

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.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving clinical benefit and has fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after careful consideration of benefit-risk balance and medical judgment by the investigator. For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Investigator's Brochure.

2.2.1.3.3. Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program (Investigator's Brochure, 2015). These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness. Expected adverse drug reactions associated with atezolizumab include the following: hepatitis/transaminitis, hypothyroidism, infusion-related reactions (IRRs), pneumonitis, influenza-like illness, and dermatologic reactions. Potential adverse drug reactions include the following: ATAs, colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion. Pericardial and pleural involvement with associated effusions is common in patients with cancer and has the theoretical potential to be exacerbated by inflammation associated with antitumor immunity following PD-L1 blockade. Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

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

2.2.1.3.4. Clinical Efficacy Summary

Patients with multiple tumor types were included in study PCD4989g, with the largest cohorts consisting of patients with non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and bladder cancer (Investigator's Brochure, 2015). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, urothelial bladder cancer (UBC), colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Objective responses were recorded for 20 of 88 (22.7%) response-evaluable patients with NSCLC, including responses in squamous and non-squamous patients (4/21 and 16/67, respectively). A total of 8 of the 20 responding NSCLC patients continued to respond at the time of the clinical data cutoff.

Analyses of tumor cells and tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for study PCD4989g, including expansion cohorts of patients with NSCLC (88 efficacy-evaluable patients), UBC (87 efficacy-evaluable patients), and RCC (62 efficacy-evaluable patients) (Powles *et al*., 2014; Herbst *et al*., 2014; Investigator's Brochure, 2015). Preliminary results suggest that PD-L1 expression in tumor-infiltrating T cells is likely to be associated with response to atezolizumab. An objective response rate (ORR) of 43% (13 of 30 patients, including 2 complete responses) was observed in UBC patients with tumor-infiltrating immune cells with PD-L1 immunohistochemistry (IHC) scores of 2 or 3, whereas the ORR among IHC 0/1 UBC patients was 11% (4 of 35) (Powles *et al*., 2014). While the median had not been reached as of January 1, 2014, the duration of response ranged from 0.1+ to 30.3+ weeks for patients with IHC 2/3 tumor-infiltrating immune populations and from 0.1+ to 6.0+ weeks for patients with IHC 0/1. Response to atezolizumab in the UBC cohort was associated with the tumor-infiltrating immune cell IHC scores (P=0.026) but not with tumor cell IHC scores (P=0.93). Similarly, a preliminary analysis of the NSCLC cohort (53 evaluable patients) and the total patient population (175 evaluable patients) of PCD4989g found that response was significantly associated with PD-L1 IHC score in tumor-infiltrating immune cells (P=0.015 in NSCLC, P=0.007 in all tumors) but not with IHC score in tumor cells (P=0.920 in NSCLC, P=0.079 in all tumors) (Herbst *et al*., 2014). Eighty-three percent of NSCLC patients with an IHC score of 3 (tumor-infiltrating immune cell) responded to treatment, whereas 43% of NSCLC patients with IHC 2 were limited to disease stabilization.

2.2.2 Bevacizumab

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity (K_d=1.1 nM) (Presta et al., 1997). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1 (Avastin™ [bevacizumab] Investigators Brochure, 2008; Kim et al., 1993; Presta et al., 1997).

2.2.2.1 Mechanism of Action

Of known proangiogenic factors, VEGF is one of the most potent and specific, and has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells *in vitro*, and decrease microvessel density and interstitial pressure in tumor xenografts *in vivo*. In patients, preliminary results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab (Willett *et al.*, 2004).

2.2.2.2 Nonclinical Studies

The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition *in vivo* in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdomyosarcoma, Calu-6, and MCF-7 cell lines (Borgstrom *et al.*, 1999; Kabbinavar, 1995; Kim *et al.*, 1993; Presta *et al.*, 1997). The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Combined blockage of the VEGF and other growth factor pathways (*e.g.*, epidermal growth factor receptor [EGFR] or Platelet Derived Growth Factor Receptor [PDGFR]) has also demonstrated additive effects *in vivo* (Bergers *et al.*, 2003; Shaheen *et al.*, 2001). Associated with the anti-tumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts as well as reduced vascular permeability and interstitial pressure.

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus monkeys administered bevacizumab, which led to reduced endometrial proliferation and uterine weight as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption, and specific gross and skeletal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia which was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits, and this effect appeared to be dose-dependent and characterized by a reduction of wound tensile strength.

2.2.2.3 Clinical Studies

Pharmacokinetics and MTD: The pharmacokinetics (PK) of bevacizumab have been characterized in several phase 1 and phase 2 clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution.

The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (Cobleigh *et al.*, 2003). The dose schedule of either 10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks is used in most phase 2 or 3 trials with only a few exceptions (*e.g.*, the pivotal phase 3 trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg every 2 weeks).

Clinical efficacy of bevacizumab: Clinical proof of principle for anti-VEGF therapy with bevacizumab has been observed in several solid tumors. In first- and second-line metastatic colorectal cancer (mCRC), the combination of bevacizumab with 5-FU-based chemotherapy improved the overall survival (OS), progression-free survival (PFS), and response rate (RR) as compared to chemotherapy alone (Hurwitz *et al.* 2004; Giantonio *et*

al., 2007). There was also improved overall survival in first-line non-small cell lung cancer (NSCLC) patients (**E4599**) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone. Bevacizumab in combination with chemotherapy has been approved by the Food and Drug Administration (FDA) for treatment in mCRC (first and second lines) and in NSCLC.

In untreated advanced and metastatic breast cancer, addition of bevacizumab to paclitaxel also significantly improved the RR and PFS (**E2100**; Miller *et al.*, 2005). However, in the phase 3 trial in doxorubicin- and paclitaxel-refractory metastatic breast cancer, the addition of bevacizumab to capecitabine did not show an improvement in PFS despite an increase in the RR (Miller *et al.*, 2002). In locally advanced and metastatic pancreatic cancer, a Phase 3 also failed to demonstrate an overall survival (OS) or PFS advantage by adding bevacizumab to gemcitabine (**CALGB-80303**) (Kindler *et al.*, 2007). Bevacizumab has been studied as monotherapy in renal cell cancer (RCC). In a three-arm, double-blind, placebo-controlled phase 2 trial (Yang *et al.*, 2003), patients with previously treated stage IV RCC were randomized to high-dose (HD) bevacizumab (10 mg/kg every 2 weeks), low-dose (LD) bevacizumab (3 mg/kg every 2 weeks), or placebo. The study demonstrated a highly significant prolongation of time to progression (TTP) in the HD arm (4.8 months) as compared with the placebo (2.6 months) (hazard ratio [HR]=2.55, *P*=0.0002); the LD arm was associated with a smaller difference in TTP (3.0 months) of borderline significance. The tumor response rate was 10% in the HD arm but 0% in the LD and placebo groups.

A Phase 3 study (**BO17705**) with bevacizumab (10 mg/kg every 2 weeks) plus interferon-α2a versus interferon-α2a plus placebo as first-line therapy in patients with advanced and/or metastatic RCC demonstrated statistically significant and clinically relevant improvements in PFS (10.2 vs. 5.4 months), and objective response rate (ORR) (31.4 vs. 12.8%).

The Phase 3 study **BO17706** indicated no statistically significant improvement in OS when bevacizumab (5 mg/kg every 2 weeks) was added to the gemcitabine/erlotinib combination in the first-line treatment of advanced pancreatic cancer. The Phase 3 NCI-sponsored **CALGB-80303** study investigating the use of bevacizumab (10 mg/kg every 2 weeks) combined with gemcitabine was prematurely terminated after the CALGB Data Safety Monitoring Board (DSMB) concluded that the futility boundary defined for the primary efficacy parameter (OS) had been crossed in a protocol-specified interim analysis (dated June 16th, 2006).

Additional clinical trials are ongoing in a variety of solid tumors and hematological malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biological agents.

2.2.2.4 Safety Profile

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events (AEs) of any severity included asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea,

dermatitis, and proteinuria. The most common grade 3-4 AEs were asthenia, pain, hypertension, diarrhea, and leukopenia.

The major bevacizumab-associated AEs identified in phase 1 to phase 3 trials include hypertension, proteinuria, arterial thromboembolic events (ATEs), hemorrhage, congestive heart failure (CHF), gastrointestinal (GI) perforations, and wound healing complications. Other serious AEs (SAEs) observed with bevacizumab therapy include reversible posterior leukoencephalopathy syndrome (RPLS) and fistula formation. The following details a description of major AEs associated with bevacizumab therapy. In addition, a list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% (all grades) across trials, with a mean increase of +5.5mmHg to +8.4mmHg for systolic pressure, or +4.1mmHg to +5.4mmHg for diastolic pressure. Incidence of grade 3 (hypertension requiring initiation of or increase in hypertensive medications) ranges from 7.8 to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 0.5% of bevacizumab-treated patients.

Hypertension associated with bevacizumab can generally be controlled with routine oral drugs while bevacizumab is continued. However, incidents of hypertensive crisis with encephalopathy (including RPLS) or cardiovascular sequelae have been rarely reported. Blood pressure (BP) should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with standard medical practice (Chobanian et al, 2003). Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from mild asymptomatic increase in urine protein (incidence of about 38%) to rare instances of grade 3 proteinuria (>3.5gm/24 hour urine) (3%) or nephrotic syndrome (1.4%). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. The risk of proteinuria may be higher in patients with advanced RCC or history of hypertension. There is also evidence from dose-finding trials that the rate of proteinuria may be dose related.

Renal thrombotic microangiopathy: Thrombotic microangiopathy (TMA) has been described in biopsy samples from case reports of patients treated with bevacizumab and other anti-VEGF agents. The presentation was mostly localized to the kidney, and systemic manifestations (e.g., thrombocytopenia or schistocytosis) were present only in

some of these patients. As renal biopsies were rarely performed in patients with proteinuria or renal insufficiency, the true rate of renal-localized or subclinical TMA is not assessable. Available data indicate that systemically evident TMA (i.e., with evidence of hemolysis or thrombocytopenia) is very rare. However, the use of more than one anti-VEGF agent in combination might enhance the risk. In a phase 1 dose escalation trial of concurrent bevacizumab (10 mg/kg every 2 weeks) and escalating doses of sunitinib (25 mg, 37.5 mg or 50 mg daily for 4 out of 6 weeks) in patients with RCC, 5 of the 12 patients at the highest dose level developed systemic TMA, or microangiopathic hemolytic anemia; clinical presentations in these cases included thrombocytopenia, schistocytes, hypertension, and varying degrees of proteinuria.

Hemorrhage: Overall, grade 3 and 4 events associated with bleeding or hemorrhage were observed in 4.0% of 1,132 patients treated with bevacizumab in a pooled database from eight phase 1, 2, and 3 clinical trials in multiple tumor types. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage - Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in patients with NSCLC. In a phase 2 study in NSCLC, 6 cases of life-threatening (4 fatal) hemoptysis were reported among 66 patients treated with bevacizumab and chemotherapy (Novotny *et al.*, 2001); squamous cell histology was identified as the risk factor. In the phase 3 trial in non-squamous NSCLC (**E4599**), the rate of Grade ≥3 broncho-pulmonary hemorrhage was <1% in the control arm (carboplatin/paclitaxel) versus 2.3% in the chemotherapy plus bevacizumab arm (10/427 patients, including 7 deaths).

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages. In the pivotal phase 3 trial in advanced CRC, the rate of GI (duodenal, ileal, cecal and colonic) hemorrhage (all grades) was 24% in the irinotecan, fluorouracil, and leucovorin (IFL)/bevacizumab arm compared to 6% in the IFL alone arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL.

Serious tumor associated bleedings have also been observed in patients with pancreatic cancer, gastric cancer, central nervous system (CNS) metastases, hepatoma, or varices treated with bevacizumab.

Mucocutaneous hemorrhage - Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention, and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Thromboembolic Events, Arterial (ATE): The risk of ATEs is increased with bevacizumab therapy; such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction (MI), and other peripheral or visceral arterial thrombosis. A

pooled analysis of five randomized studies showed a two-fold increase in these events (3.8% vs. 1.7%). ATE led to a fatal outcome in 0.8% patients with bevacizumab (vs. 0.5% without bevacizumab). The rate of cerebrovascular accidents (including TIA) was 2.3% vs. 0.5%, and the rates of MI 1.7% vs. 0.7%. Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk (Skillings *et al.*, 2005). In patients ≥65 years treated with bevacizumab and chemotherapy, the rate of ATE was approximately 8.5%.

Aspirin is a standard therapy for primary and secondary prophylaxis of ATE in patients at high risk of such events, and the use of aspirin ≤325 mg daily was allowed in the five randomized studies discussed above though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and ATE events, retrospective analyses of the ability of aspirin to affect the risk of ATE were inconclusive. Further analyses of the effects of concomitant use of bevacizumab and aspirin are ongoing.

Thromboembolic Events, Venous (VTE) (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): In the phase 3 pivotal trial in mCRC, there was a slightly higher rate of VTE in patients treated with chemotherapy plus bevacizumab compared with chemotherapy alone (19% vs. 16%). The incidence of NCI-CTC Grade≥3 VTEs in one NSCLC trial (**E4599**) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%).

In clinical trials across all indications, the overall incidence of VTEs ranged from 2.8% to 17.3% in the bevacizumab-containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE compared with chemotherapy alone. However, patients with mCRC who receive bevacizumab and experienced VTE may be at higher risk for recurrence of VTE.

Perforations of GI tract: GI perforations/fistula are rare but have occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention, and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (**AVF2107**), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving fluorouracil (5-FU)/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in non-CRC tumors (*e.g.*, gastric/esophageal, pancreatic, and ovarian cancers) or nonmalignant conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

GI Fistula: Fistula formations, including events resulting in death, have been observed in patients receiving bevacizumab in clinical studies and post-marketing reports. Fistulae in the GI tract are common (1-10% incidence) in patients with certain metastatic tumors such as CRC or cervical, but uncommon (0.1-1%) or rare (0.01-0.1%) in other indications.

In GOG 240, the rate of GI vaginal fistula was 8.2%.

In addition, fistulae that involve areas other than the GI tract have also been observed (e.g. tracheoesophageal, bronchopleural, urogenital, and biliary). Events were reported at various time points during treatment, ranging from 1 week to >1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy. Tracheoesophageal (TE) fistula: Life-threatening or fatal TE fistula has been reported in patients with small cell lung cancer (SCLC) treated with concurrent chemoradiation and bevacizumab. In a phase 2 trial of bevacizumab plus irinotecan, carboplatin, and radiation therapy (RT) followed by maintenance bevacizumab that accrued 25 patients, there have been two confirmed cases of TE fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of chemoradiation). While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without RT), the incidence was extremely low.

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. Across mCRC trials, at least 28 days must have elapsed following major surgery before bevacizumab could be initiated; data suggested initiation of bevacizumab 29-60 days following surgery did not appear to increase the risk of wound healing complications compared to those treated with chemotherapy alone.

The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined. In the pivotal study in CRC, among patients who underwent major surgery while on study therapy, there was an increased rate of significant post-operative bleeding or wound healing complications in the IFL plus bevacizumab arms vs. IFL alone [10% (4/40) vs. 0% (0/25)] (Scappaticci *et al.,* 2005). Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, range 11-50 days).

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

Heart failure (HF): The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 trials in metastatic breast cancer (**AVF 2119g**) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 3% in the bevacizumab plus capecitabine arm compared to 1% in the capecitabine-only arm (Miller et al. 2005). In a

Phase 3 trial of patients with previously untreated metastatic breast cancer (**E2100**), the incidence of left ventricular ejection fraction (LVEF) decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel plus bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

In phase 2 study of 48 patients with refractory acute myelogenous leukemia treated with cytarabine, mitoxantrone, and bevacizumab, five cases of cardiac dysfunction (CHF) or LVEF decreases to <40% were reported. All but one of these subjects had significant prior exposure to anthracyclines as well. Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin (cumulative doses at 240 mg/m^2), and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to <40% (Wedam *et al.*, 2006). In a small phase 2 study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m^2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m^2 and one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m^2); an additional 4 patients had asymptomatic decreases in LVEF (D'Adamo et al. 2004). Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline Multi Gated Acquisition Scan (MUGA) or echocardiogram (ECHO) with a normal ejection fraction.

<u>Reversible Posterior Leukoencephalopathy Syndrome (RPLS), Posterior Reversible Encephalopathy Syndrome (PRES), or similar leukoencephalopathy syndrome</u>: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, visual disturbance or cortical blindness, with or without associated hypertension. MRI scans are required for diagnosis. [Typical findings are vasogenic edema (enhanced intensity in T2 and FLAIR sequences on non-contrast magnetic resonance imaging [MRI]) predominantly in the white matter of the posterior parietal and occipital lobes, and less frequently, in the anterior distributions and the gray matter].

RPLS/PRES is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known (Glusker *et al.,* 2006; Ozcan *et al.,* 2006).

<u>Neutropenia</u>: In the phase 3 trial with IFL plus or minus bevacizumab in CRC, Grade 3-4 neutropenia was 21% with bevacizumab plus IFL vs. 14% with IFL alone (Grade 4 neutropenia was 3% vs. 2%). Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab. In a phase 3 trial in NSCLC, the carboplatin and paclitaxel plus bevacizumab arm was associated with increased rate of Grade 4 neutropenia (27% vs. 17%), febrile neutropenia (5.4% vs. 1.8%), and infection with neutropenia (4.4% vs. 2.0%) with three fatal cases (Sandler *et al.*, 2006).

Bone metaphyseal dysplasia in children with active (open) growth plates: Inhibitors of VEGF/VEGFR pathways have been shown to induce physeal dysplasia in juvenile cynomolgus monkeys with open growth plates. Asymptomatic metaphyseal bone lesions were also observed in a 4.5-month old infant after 4 doses (8 weeks) of bevacizumab for treatment of cutaneovisceral angiomatosis with thrombocytopenia (CAT). The radiographic findings included lytic lesions in the metaphyses of upper and lower extremity long bones, which reversed following cessation of bevacizumab (Smith *et al,* 2008). In a phase 1 pediatric study with bevacizumab, metaphyseal expansion was not observed in the three patients with open growth plates at baseline; however, the duration of treatment was limited (Bender *et al.,* 2008). At this time, experience is limited for prolonged treatment with bevacizumab in children, and no data are available for the long term impact of bevacizumab on growth.

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

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, ranging from 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

2.3 Rationale

Preclinical data illustrate the immunosuppressive effects of VEGF, which are reversed by VEGF blockade. VEGF is thought to induce myeloid derive suppressor cells (MDSC), which suppress the anti-tumor T-cell and dendritic cell response (http://www.ncbi.nlm.nih.gov/pubmed/22437938). VEGF blockade may increase T cell trafficking to tumors, increase anti-tumor populations of T cells (CD8+ and CD4+ central memory) and decrease pro-tumor immune populations (myeloid-derived suppressor cells and regulatory T cells) (http://www.ncbi.nlm.nih.gov/pubmed/18566400, http://www.ncbi.nlm.nih.gov/pubmed/24018532, http://www.ncbi.nlm.nih.gov/pubmed/17606729, http://www.ncbi.nlm.nih.gov/pubmed/20631075). In addition, anti-VEGF therapies may reduce suppressive cytokines, tumor-infiltrating T regulatory cells and MDSC (http://www.ncbi.nlm.nih.gov/pubmed/19888452).

Several clinical studies have illustrated the potential advantage of adding anti-angiogenic agents to checkpoint blockade therapy. A Phase II study of bevacizumab with the anti-CTLA-4 agent ipilimumab in melanoma showed a DCR of 67.4% and median survival of 25.1 months, which was substantially better than historical controls. Furthermore, on-treatment biopsies exhibited inflammation and lymphocyte infiltration (http://www.ncbi.nlm.nih.gov/pubmed/24838938). In a Phase Ib study of 12 patients with renal cell carcinoma treated with bevacizumab and atezolizumab, 40% had an objective response, which appeared to occur independent of PD-L1 IHC staining (Figure 1, McDermott et al, ESMO 2014, Abstract 809O; Sznol et al, JClin Oncol 33, 2015 Abstract 410). A phase III trial is in progress (A phase III, open label, randomized study of atezolizumab [anti-PD-L1 antibody] in combination with bevacizumab versus sunitinib in patients with untreated advanced renal cell carcinoma). Renal cell carcinomas (RCC), like cervix cancers, do not harbor a particularly high mutational burden, and are treated with bevacizumab as a standard of care.

The combination of atezolizumab and bevacizumab has already provided an excellent safety signal. In Study GP28328, the grade 3-5 AE rate was 1/35 patients (2.9%). The one >= grade 3 event was neutropenia.

2.4 Correlative Studies Background

2.4.1 PD-L1 Expression (integrated biomarker)

The expression of PD-L1 has been previously demonstrated to be associated with improved clinical benefit from therapies targeting the PD-1/PD-L1 pathway (reviewed in https://www.ncbi.nlm.nih.gov/pubmed/24714771). The utility of PD-L1 expression as a predictive biomarker, however, has been debated as it is highly dynamic and can be up-regulated in response to immune activating factors. In this trial, tumor and immune cell PD-L1 staining will be evaluated by immunohistochemistry (IHC) in formalin-fixed, paraffin-embedded (FFPE) tumor tissue from an archived sample and a pre-treatment biopsy per patient. In patients in whom biopsy tissue is insufficient, this evaluation will be performed only on archived tissue. If responses occur predominantly in patients with PD-L1 positive tumors, this would suggest it should be explored in larger studies; whereas, if there no association between PD-L1 and response, this would suggest either the sample size was too small to detect the association, or that there is not a strong association.

2.4.2 TCR sequencing (exploratory biomarker)

TCR sequencing (TCRSeq) will be performed on the tumor and peripheral blood mononuclear cells (PBMC) at baseline. Genomic DNA will be purified from total PBMCs; FFPE slides from pre-treatment tumor biopsy samples will be used for intratumoral TCR sequencing. If biopsy tissue is insufficient, archived tissue may be used. The TCRCDR3 regions will be amplified and sequenced using ImmunoSEQ technology (Adaptive Biotechnologies, Seattle, WA) as previously described (https://www.ncbi.nlm.nih.gov/pubmed/19706884). If baseline intratumoral or peripheral TCR clonality associates with response to therapy, as has been seen in other solid tumors, this could provide a complementary or improved biomarker relative to PD-L1. If no such

association were seen, this would suggest either the sample size was too small to detect the association, or that there is not a strong association.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have measurable disease per RECIST 1.1. See Section 11 for the evaluation of measurable disease.

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis.

3.1.2 Patients must have had one prior systemic chemotherapeutic regimen for management of recurrent, persistent or metastatic carcinoma of the cervix (e.g.; paclitaxel/cisplatin, paclitaxel/cisplatin/bevacizumab), at least one of which must have contained bevacizumab

NOTE: Patients are allowed to receive 1-2 two prior regimens for management of recurrent, persistent or metastatic carcinoma of the cervix. Patients who have received more than two prior systemic regimens for management of recurrent, persistent or metastatic carcinoma of the cervix are NOT eligible.

NOTE: Prior adjuvant therapy is NOT counted as a systemic chemotherapeutic regimen for management of recurrent, persistent or metastatic carcinoma of the cervix. Adjuvant therapy includes cisplatin given concurrent with primary radiation therapy (CCRT) and adjuvant chemotherapy given following the completion of concurrent chemotherapy and radiation therapy (e.g., paclitaxel and carboplatin for up to 4 cycles).

3.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of atezolizumab in combination with bevacizumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Patients must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥9 g/dL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN) (however, patients with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)
– AST(SGOT)/ALT(SGPT)	≤3 × ULN

– alkaline phosphatase	≤2.5 × ULN
– creatinine	≤1.5 × ULN
– INR and aPTT	≤1.5 × ULN (This applies only to patients who **do not** receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation, such as low-molecular-weight heparin or warfarin, should be on a stable dose.)
– urine protein	Must be screened by urinalysis. If protein is 2+ or higher, 24-hour urine protein should be obtained and the level should be <1000 mg for patient enrollment.

3.1.6 Patient must have recurrent, persistent or metastatic cervical cancer including squamous cell, adenocarcinoma and adenosquamous histologies. Mesonephric carcinoma, minimal deviation/adenoma malignum, clear cell carcinoma and gastric type are excluded.

3.1.7 Administration of atezolizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of atezolizumab.

Bevacizumab is detrimental to fetal growth. For this reason and because anti-VEGF inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, fertile women must agree to use adequate contraceptive measures during study therapy and for at least 6 months after the completion of bevacizumab therapy.

Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 Tumors within previous radiated field will be designated "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.10 Willingness to undergo a tumor biopsy.

3.2 Exclusion Criteria

3.2.1 Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

3.2.2 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events (other than alopecia) due to agents administered more than 4 weeks earlier. However, the following therapies are allowed:

- Hormone-replacement therapy or oral contraceptives

- Herbal therapy >1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)

3.2.3 Prior treatment with anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents.

3.2.4 Prior treatment with anti-CTLA-4 therapeutic antibody or pathway-targeting agents.

3.2.5 Treatment with any other investigational agent within 4 weeks prior to Cycle 1, Day 1.

3.2.6 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-α or interleukin [IL]-2) within 6 weeks) prior to Cycle 1, Day 1.

3.2.7 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

- Patients who have received acute, low dose, systemic immunosuppressant medications (*e.g.*, a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.2.8 Patients taking bisphosphonate therapy for symptomatic hypercalcemia. Use of bisphosphonate therapy for other reasons (*e.g.*, bone metastasis or osteoporosis) is allowed.

3.2.9 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

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

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

3.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab or atezolizumab.

3.2.13 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.

- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) <u>are eligible</u>.
- Patients positive for hepatitis C virus (HCV) antibody <u>are eligible only if</u> polymerase chain reaction (PCR) is negative for HCV RNA.

3.2.14 History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (*e.g.*, patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids (*e.g.*, hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
  - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.2.15 History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (*i.e.*, bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) <u>is permitted</u>.

3.2.16 Patients with active tuberculosis (TB) are excluded.

3.2.17 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.

3.2.18 Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1.

3.2.19 Received oral or intravenous (IV) antibiotics within 2 weeks prior to Cycle 1, Day 1. Patients receiving prophylactic antibiotics (*e.g.*, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

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

3.2.21 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 and up to 5 months after the last dose of aztezolizumab.

- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated

influenza vaccine within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

3.2.22 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.23 Patients positive for human immunodeficiency virus (HIV) are NOT excluded from this study, but HIV-positive patients must have:

a. A stable regimen of highly active anti-retroviral therapy (HAART)
b. No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
c. A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests

3.2.24 Pregnant women are excluded from this study because atezolizumab and/or bevacizumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab and/or bevacizumab, breastfeeding should be discontinued if the mother is treated with atezolizumab and/or bevacizumab.

3.2.25 Malignancies other than the cervical cancer within 5 years prior to cycle 1, day 1, with the exception of those with a negligible risk of metastasis or death, such as adequately controlled basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the breast.

3.2.26 Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.

3.2.27 Patients with clinically significant cardiovascular disease are excluded.

- Inadequately controlled HTN (SBP ≥160mmHg and/or DBP ≥90 mmHg despite antihypertensive medication)
- History of CVA within 6 months
- Myocardial infarction or unstable angina within 6 months
- New York heart association class II or greater congestive heart failure
- Serious and inadequately controlled cardiac arrhythmia
- Significant vascular disease (e.g. aortic aneurysm, history of aortic dissection)
- Clinically significant peripheral vascular disease

3.2.28 History of abdominal/pelvic fistula, gastrointestinal perforation and/or intraabdominal abscess within 6 months prior to day 1.

3.2.29 Evidence of bleeding diathesis or clinically significant coagulopathy.

3.2.30 Serious or non-healing wound, active ulcer or bone fracture.

3.2.31 Patients requiring treatment with a RANKL inhibitor (e.g. denosumab) who cannot discontinue it before treatment with atezolizumab.

3.3 Inclusion of Minorities

NIH policy requires that members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	0	0	0	**2**
Native Hawaiian or Other Pacific Islander					
Black or African American	2	0	2	0	**4**
White	12	0	2	0	**14**
More Than One Race	1	0	1	0	**2**
Total	**17**	**0**	**5**	**0**	**22**

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4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (*i.e.*, all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (*i.e.*, all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *NCI protocol #10010* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MD017, and protocol *NCI Protocol # 10010*.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will automatically load to RSS.)

4.2.2 Requirements For *NCI protocol #10010* Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal (**Note**: Use of the Regulatory Submission Portal will be **mandatory** beginning in early 2017.)
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

4.2.4 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Enrolled patients with initiate treatment with atezolizumab and bevacizumab beginning Day 1 of Cycle 1. A cycle is 21 days. See below for details regarding administration of each agent. Atezolizumab will be administered first, followed by bevacizumab.

While on study, patients will return for assessments every week during the first cycle, then every 3 weeks.

Patients that require discontinuation of one study agent (atezolizumab or bevacizumab), but meet criteria to continue the other study agent (atezolizumab or bevacizumab) may do so after discussion with the study chair.

During screening, every 9 weeks (+/- 7 days) for the first year then every 12 weeks (+/-7 days), and at the end of study, patients will have a CT or MRI of the abdomen and pelvis and a CT of the chest performed.

A patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

It will be acceptable for a new cycle of therapy (and all associated tests and procedures) to be delivered within a 3 day window before and after the protocol defined date.

5.1.1 Atezolizumab

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

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Anaphylactic precautions should be observed during atezolizumab administration. Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. The management of Infusion Related Reactions will be according to severity as per Table 6: Management Guidelines for Infusion-Related Reactions.

5.1.2 *Bevacizumab*

Bevacizumab is administered by intravenous (IV) infusion. The dose should be based on the patient's actual body weight; the dose will be recalculated if there is a weight change of >10% from baseline.

Bevacizumab doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

The first dose of bevacizumab should be given over 90 minutes. If well tolerated, the second dose can be given over 60 minutes. If this dose is well-tolerated, then all subsequent infusions can be administered over 30 minutes. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well tolerated.

Special Precautions/Safety Issues:
Prior to each treatment, the patient should be carefully assessed with special attention to

BP, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and RPLS. Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines.

Patients who have an ongoing study agent-related SAE upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

Infusional reactions: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids, or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.

Hypertension: Patients should have BP monitored prior to each infusion of bevacizumab. Hypertensive mediation should be initiated or increased for optimal BP control according to standard public heath guidelines.

Proteinuria: Proteinuria should be monitored per protocol.

Surgery and wound complication issues and surgery: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.

5.1.3 Other Modality(ies) or Procedures

N/A

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Atezolizumab General Concomitant Medication Guidelines

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

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive

therapies as clinically indicated (*e.g.*, supplemental oxygen and β_2-adrenergic agonists; see **Section 5.1.1**).

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

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see **Section 3.2**) should continue their use. Females of reproductive potential should use highly effective means of contraception.

5.2.2 **Atezolizumab Excluded Therapies**

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

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in **Section 3.2** and **Section 5.2.1**).

It is strongly recommended that:

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

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

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

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

treating physician. If feasible, alternatives to these agents should be considered.

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

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for an unlimited number of cycles or until one of the following criteria applies:

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

5.3.1 Treatment Beyond Progression

Refer to **Appendix B** for samples.

Treatment may be continued in cases of radiologic progression at the first 9 week (+/- 7 days) CT if all of the following criteria are satisfied:

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesions (including up to 4 new lesions added to the sum)
- No more than 4 new lesions included in the sum.

NOTE: If treatment is continued in the case of radiologic progression at the first 9 week (+/- 7 days) CT, a reassessment scan must be performed at 4 weeks (+/- 7 days) to rule out ongoing progression.

For patients who continue treatment in the case of radiologic progression at the first 9 week (+/- 7 days) CT:

- At any subsequent CT scan patients who have stable disease as compared to the 9 week (+/- 7 days) CT scan will be allowed to continue on study treatment.
- Patients who continue treatment in the case of radiologic progression at the first 9 week (+/- 7 days) CT, and later experience a PR or CR (as compared to baseline CT) will be recorded as delayed responses.

5.4 Duration of Follow Up

Patients will be followed for vital status every 3 months for two years, after removal from treatment or until death, whichever occurs first. The every three month follow up for two years can be by phone call or clinic visit. Follow-up will cease when study is terminated. Patients removed from treatment for unacceptable adverse event(s) will be followed until resolution or

stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from treatment when any of the criteria listed in Section 5.3 applies. The reason for treatment and study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

NOTE: Patients that require discontinuation of one study agent (atezolizumab or bevacizumab), but meet criteria to continue the other study agent (atezolizumab or bevacizumab) may do so after discussion with the study chair.

NOTE: Upon occurrence of perforation and/or fistula (defined below) study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours. CTEP will be notified within 7 days of study chair notification of each instance of perforation and/or fistula. The study chair will consult CTEP and the study statistician to review the history of the affected patient and the perforation and/or fistula toxicities for the trial as a whole before proceeding with the recommendation to resume protocol therapy for the affected patient with single agent atezolizumab. Per section 6.2.2 below, bevacizumab must be discontinued for perforation (GI, or any other organ), any grade AND/OR fistula (GI, pulmonary or any other organ), any grade.

Definition of perforation and fistula:

- Perforation (GI, or any other organ), any grade
- Fistula (GI, pulmonary or any other organ), any grade

6.1 Atezolizumab (MPDL3280A)

6.1.1 General AE Management and Dose Modification Guidelines

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Please note: Tumor measurements must continue on schedule (see study calendar, section 10.1) during temporary suspension (Tumor measurements are repeated every 9 weeks (+/- 7 days) for 12 months, then every 12 weeks (+/- 7 days) thereafter.). Patients with progression will be discontinued from study treatment.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the study PI in consultation with CTEP.

Atezolizumab must be **permanently discontinued** if the patient experiences any of the following events, regardless of benefit:

- Grade 4 pneumonitis
- AST or ALT >5×ULN or total bilirubin >3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Grade 4 ocular inflammatory toxicity
- Grade 4 pancreatitis or any grade of recurrent pancreatitis
- Grade 4 rash
- Any grade myocarditis

Treatment may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, but only after consultation with the trial Principal Investigator:

- Grade 3 pneumonitis
- Grade 3 ocular inflammatory toxicity
- Grade 3 or 4 infusion-related reactions

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo *et al.*, 2010). Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab.
For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Investigator's Brochure and the FDA product label.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the 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 irAEs.

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

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, in the absence of an alternative etiology, 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, contact the Principal Investigator for additional recommendations.

6.1.2 Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See **Table 6** for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
- Atezolizumab may be held for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

1. 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.

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

Table 1: Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 2	• Withhold atezolizumab. • 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. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Study Chair. [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.
Myocarditis All grades	• Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.

BAL = bronchoscopic alveolar lavage; IVIG = intravenous immunoglobulin

[a] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

2. Hepatic Events

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

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

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

Table 2: Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Study Chair.[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] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

3. Gastrointestinal Events

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

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

Table 3: Management Guidelines for Gastrointestinal Events

Event	Management
Acute abdominal pain	• Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for "Amylase and/or lipase increase" and "Immune-related pancreatitis" elsewhere in this table, as needed. • Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity (see the "Hepatotoxicity" guideline elsewhere in this table).
Diarrhea or colitis, Any grade	• Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. • All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g.*, increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
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. • 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. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a,b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks. [a,b,c]

Diarrhea or colitis, Grade 3	• Withhold atezolizumab. • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c]

Table 3: Management Guidelines for Gastrointestinal Events (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Study Chair. Patient may not resume treatment, regardless of benefit. • Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day intravenous 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] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

4. Endocrine Events

Thyroid disorders or adrenal insufficiency has been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Table 4: Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism, Grade 1	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism, Grade 2+	• 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, Grade 1	**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, Grade 2+	• 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 and contact Study Chair for life-threatening immune-related hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab.[a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab if event resolves to Grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks.[a, b, c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.

Table 4: Management Guidelines for Endocrine Events (cont.)

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.

TSH = thyroid-stimulating hormone;

[a] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

5. Ocular events

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

Table 5: Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Study Chair. [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] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

6. Infusion-Related Reactions

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in Table 6. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 6: Management Guidelines for Infusion-Related Reactions

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

IRR = infusion-related reaction; IV = intravenous.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event.

7. 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, are provided in Table 7.

Table 7: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase increased, Grade 1	• Continue atezolizumab • Monitor amylase and lipase prior to dosing
Amylase and/or lipase increased, 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 increased, Grade 3 or 4	• Hold atezolizumab. • Refer patient to gastrointestinal (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 within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. • Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. • For recurrent events, permanently discontinue atezolizumab.[c]
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c] • For recurrent events, permanently discontinue atezolizumab and contact Study Chair.[c]

Table 7: Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Study Chair. [c] • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous 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] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

8. Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 8.

Table 8: Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	• Withhold atezolizumab. • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Study Chair.[c]
Persistent and/or severe rash or pruritus, any grade	• A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated.

[a] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

9. Neurologic disorders

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

Table 9: Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Evaluate for alternative etiologies.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab. • Evaluate for alternative etiologies. • Initiate treatment as per institutional guidelines. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Study Chair if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Study Chair. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Study Chair. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or intravenous prednisone or equivalent.

[a] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent.

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

10. Immune-related meningoencephalitis

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10: Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Study Chair. [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 resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

IV = intravenous.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event.

The safety profile remains consistent based on the known mechanism of action of atezolizumab. As more data are generated in atezolizumab's growing clinical development plan, further updates will be provided on the incidence of these adverse events in patients taking atezolizumab. As with all investigational products, unknown side effects may occur. Patients should be monitored closely throughout their participation in clinical studies with atezolizumab.

6.2 Bevacizumab

6.2.1 General AE Management and Dose Modification Guidelines

There will be no dose reduction for bevacizumab in this study. Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab is interrupted for ANY reasons for >4 weeks (unless otherwise specified), the patient should discontinue bevacizumab therapy on protocol.

6.2.2 Management of Specific AEs

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
Allergic reactions Or **Infusion-related reactions** Or **Anaphylaxis**	Grade 1-2	• Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. • For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. • Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial), arterial ischemia - Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - Any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Venous)		
	Grade 3 OR asymptomatic Grade 4	• Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: • The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) • The subject must not have had hemorrhagic events while on study • The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab.

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
		• If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mmHg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg) • Grade 3 (SBP ≥160 mmHg or DBP ≥100 mmHg)	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg • For hypertension that is refractory requiring delay of bevacizumab for > 4 weeks, discontinue bevacizumab
	Grade 4 (Hypertensive crisis or malignant hypertension)	Discontinue bevacizumab
Heart Failure OR **Left Ventricular (LV) dysfunction**	• Heart failure ≥Grade 2 • LV dysfunction ≥Grade 3	Discontinue bevacizumab
Proteinuria Proteinuria will be monitored by urine analysis dipstick. If Dipstick ≥2+ proteinuria, 24-	Dipstick ≥ 2+	Hold bevacizumab and obtain 24 hour urine protein
	If 24-h urine protein <2g	Continue bevacizumab

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
hour urine protein should be obtained	If 24-h urine protein ≥2 g	• Hold bevacizumab until 24-hour urine protein <2.0 g • Discontinue bevacizumab if urine protein does not recover to < 2.0 g after 8 weeks of bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold 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 could increase the risk of hemorrhage recurrence
Hemorrhage (not CNS or pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold 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 could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome OR	Any Grade	Discontinue bevacizumab upon diagnosis of RPLS.

Treatment Modification for Bevacizumab-Related Adverse Events		
Event	**CTCAE. V4 Grade**	**Action to be Taken**
PRES (Posterior Reversible Encephalopathy Syndrome)		
Wound dehiscence OR **Wound complications**	Grade 2	Hold bevacizumab until healing
	Grade 3-4	Discontinue bevacizumab
Perforation (GI, or any other organ)	Any Grade	Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)	Any Grade	Discontinue bevacizumab
Obstruction of GI tract	Grade 2 requiring medical intervention	Hold bevacizumab until complete resolution
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after 28 days and full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to≤Grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the Grade 4 toxicity is transient, has recovered to ≤Grade 1 and unlikely to recur with retreatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2 **and 7.3**) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are

protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1369 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 Atezolizumab

Version 2.1, June 7, 2017[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 4.0 Term) [n= 1369]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
		Endocrine disorders - Other (hypophysitis)[2]	
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 4.0 Term) [n= 1369]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
	Infusion related reaction[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFECTATIONS			
		Meningitis[2]	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
	GGT increased[2]		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
		Generalized muscle weakness	
	Myalgia[2]		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (Guillain-Barre syndrome)[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 4.0 Term) [n= 1369]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (myasthenia gravis)[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		

*Denotes adverse events that are <3%.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

CARDIAC DISORDERS - Cardiac arrest

GASTROINTESTINAL DISORDERS - Constipation; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE conditions - Chills; Edema limbs; Malaise; Pain
INFECTIONS AND INFESTATIONS - Lung infection; Sepsis; Urinary tract infection
INVESTIGATIONS - Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 Bevacizumab

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome[2]	
	Cardiac disorders - Other (supraventricular arrhythmias)[3]		***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)***
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[2]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	

		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fasciitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Injury, poisoning and procedural complications – Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Cardiac troponin I increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[11]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[12]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	

		Ischemia cerebrovascular[2]	
	Peripheral sensory neuropathy[13]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
	Proteinuria		***Proteinuria (Gr 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[14]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***
		Vascular disorders - Other (arterial thromboembolic event)[2,15]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3]Supraventricular arrhythmias may include supraventricular tachycardia, atrial

fibrillation and atrial flutter.
[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.
[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak
[11]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.
[12]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.
[13]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.
[14]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[15]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack and stroke.
Also reported on bevacizumab (rhuMAb VEGF) trials but with the relationship to bevacizumab (rhuMAb VEGF) still undetermined:
BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive

cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Generalized muscle weakness; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous

system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis
Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Pregnancy loss is defined in CTCAE as "Death in utero." Any pregnancy loss should be reported expeditiously, as **Grade 4 "Pregnancy loss"** under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Adverse Events of Special Interest in Atezolizumab Studies

The following AEs are considered of special interest in patients receiving atezolizumab and must be reported expeditiously through CTEP-AERS, irrespective of regulatory seriousness criteria:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, hypophysitis, and adrenal insufficiency
- Hepatitis
- ALT >10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, or infusion related reactions
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Loading of the pathology report is required.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Atezolizumab (NSC 783608)

Other Names: MPDL3280A

Classification: monoclonal antibody

M.W.: 150 KD

Mode of Action: anti-PD-L1

Description:
Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007).

How Supplied:
Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. 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.

Preparation:
The prescribed dose of atezolizumab should be diluted in 250 mL 0.9% NaCl and infused through a 0.2 micrometer in-line filter. The IV bag may be constructed of PVC or PO; the IV infusion line may be constructed of PVC or PE; and the 0.2 micrometer in-line filter may be constructed of PES. The prepared solution may be stored at 2°C-8°C or room temperature for up to 8 hours.

Storage:
2°C-8°C (36°F-46°F) Vial contents should not be frozen or shaken and should be protected from direct sunlight.

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

Route of Administration: IV infusion

Method of Administration:
Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

Potential Drug Interactions:
Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

Patient Care Implications:
Male and female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 5 months (150 days) after the last dose of atezolizumab.

Availability:
Atezolizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.2 Bevacizumab (NSC 704865)

Other Names: rhuMAb VEGF, Avastin®

Classification: Recombinant humanized monoclonal antibody

MW: Approximate molecular weight is 149,000 daltons

Mode of Action:
Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

Description:
Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions.

How Supplied:
Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP**.**

Preparation:
Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection**.**

Storage:
Upon receipt, refrigerate bevacizumab (2° to 8° C). Do not freeze. Do not shake.

Stability:
Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry. Once diluted in 0.9% sodium chloride, administer solutions of bevacizumab within 8 hours**.**

Route of Administration: Intravenous

Method of Administration:
Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

Availability:
Bevacizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Biosketch/Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday

between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Exploratory/Ancillary Correlative Studies

9.1.1 *PD-L1 Immunohistochemistry and T-cell Receptor Sequencing*

9.1.1.1 Collection of Specimen(s)

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the biospecimen type (primary, metastatic, recurrent, persistent). Primary (FP01) and metastatic (FM01) tumor should be collected prior to all treatment. Recurrent and persistent tumor should be collected prior to the study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled recurrent primary (FRP01) or persistent primary (FPP01), respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled recurrent metastatic (FRM01) or persistent metastatic (FPM01), respectively. Only one block may be submitted per tissue type.

Biopsy tissue sampling instructions and requirements: A minimum of one core biopsy sample should be attained, for the purposes of Hematoxylin and eosin (H and E) staining, PD-L1 IHC and TCR sequencing. Bone metastases, final needle aspirates, cytology specimens and alcohol-fixed specimens are not suitable for PD-L1 IHC or TCR sequencing.

For both archived and fresh biopsy tissue, every attempt should be made to provide a block; however, if a block cannot be provided then unstained slides (9 charged, 4 µm) should be submitted. For PD-L1 staining, 4 charged, 4µm, sections must be cut fresh and only shipped when requested by the study team. Blocks or fresh cut (not older than 60 days) sections of FFPE tumor will be shipped to a designated CLIA laboratory upon closure of each trial phase. For the H&E, one of the 9 slides is needed, and for TCR sequencing 4 of 9 slides are needed. The H and E slides will be collected and reviewed for tumor content by a pathologist.

Peripheral blood will be collected prior to the first dose of therapy; genomic DNA will be purified from total PBMCs. PBMC DNA will be isolated from whole blood for TCR sequencing according to the following steps: 7-10mL of blood should be drawn into a lavender/purple top tube(s) labeled with the patient's study ID. A minimum of 3mL is needed for processing. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA. Ship whole blood to the address below on the day the biospecimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) and shipped within 24 hours.

Dr. Friedman and colleagues will isolate whole blood DNA from these samples. DNA will then be shipped to Adaptive Biotechnologies for sequencing.

The slides of tumor tissue for TCR sequencing will be sent to Adaptive Biotechnologies for DNA isolation, sequencing and data generation. The TCRCDR3 regions will be amplified and

sequenced using ImmunoSEQ technology (Adaptive Biotechnologies, Seattle, WA) as previously described (https://www.ncbi.nlm.nih.gov/pubmed/19706884). In brief, bias-controlled V and J gene primers are used to amplify rearranged V(D)J segments for high-throughput sequencing. After correcting sequencing errors via a clustering algorithm, CDR3 segments are annotated to identify the V, D, and J genes that contributed to each rearrangement. The estimated TIL content will be calculated as previously described (https://www.ncbi.nlm.nih.gov/pubmed/25428505). For each sample, Shannon entropy will be calculated on the clonal abundance of all productive TCR sequences in the data set.

The type of biospecimen (block, slides) should be specified. If submitting slides, the slide type, thickness, and count should also be specified.

Labeling formalin-fixed, paraffin-embedded tissue
A waterproof permanent marker or printed label should be used to label each translational science biospecimen with:
NCI Protocol number 10010
Biospecimen code (see above)
Collection date (mm/dd/yyyy)
Surgical pathology accession number
Block number

Note: if labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

9.1.1.2 Shipping of Specimen(s)

Pre-treatment blood samples are to be shipped to:

Rosemarie Ramsawak/Kevin Crawford/Phillip Wong
Immune Monitoring Facility, Room ZRC-1513
Memorial Sloan Kettering Cancer Center
408 East 69th Street
New York, NY 10021
Lab Phone 1: 1-646-888-2114
Lab Phone 2: 1-646-888-3106

Fresh pre-treatment biopsies and archived tissue is to be shipped to:

Merghoub Lab
C/O: Beatrice Yin
417 E 68th St
Rm: Z1525
New York, NY 10065

9.1.1.3 Site(s) Performing Correlative Study

Claire Friedman, MD
Memorial Sloan Kettering Cancer Center
300 E. 66th Street
New York, NY 10065
646-888-4247
friedmac@mskcc.org

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Baseline radiographic tumor assessment must be done within 30 days prior to the start of therapy. Patients receiving atezolizumab and bevacizumab will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment. It will be acceptable for a new cycle of therapy (and all associated tests and procedures) to be delivered within a 4 day window before and after the protocol defined date (see section 5.1). If screening laboratory assessments are performed within 4 days prior to Cycle 1, Day 1 they do not need to be repeated at Cycle 1, Day 1.

	Pre-Study	Cycle 1, Day 1 (week 1) +/- 4 days	Cycle 1, Wk 2 +/- 4 days	Cycle 1, Wk 3 +/- 4 days	Cycle 2, Day 1 +/- 4 days	Cycle 3, Day 1 +/- 4 days	Cycle 4+, Day 1 +/- 4 days	Off Study[c]
Atezolizumab		A			A	A	A	
Bevacizumab		B			B	B	B	
Informed consent[g]	X							
Demographics	X							
Medical history	X							
Concurrent meds	X	X----------	----------	----------	----------	----------	----------X	X
Physical exam	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Height	X							
Weight	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X
PT (INR)/PTT	X							

TSH	X				X	X	X	
Urinalysis[d]	X					X		
EKG	X							
Adverse event evaluation		X----------X						X
Tumor measurements	X	Tumor measurements are repeated every 9 weeks (+/- 7 days) for 12 months, then every 12 weeks (+/- 7 days) thereafter. Documentation (radiologic) must be provided for patients removed from treatment for progressive disease.[f]						X
B-HCG	X[b]							
Archived FFPE Submission[e]	X[e]							
Pre-Treatment Biopsy	X[e]							
Pre-Treatment Research Blood	X[e]							

A: Atezolizumab 1200mg IV

B: Bevacizumab 15mg/kg IV

a: Na, K, Cl, CO2, BUN, creatinine, Ca, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT

b: Serum pregnancy test (women of childbearing potential).

c: Off-study evaluation (30 days +/- 7 days after last dose)

d: Urinalysis for urine protein prior to every other cycle (odd cycles, e.g., prior to Cycle 3, 5, 7, ect)

e: Pre-treatment biopsy formalin fixed paraffin embedded (FFPE) should be submitted for each patient. If pre-treatment biopsy results in insufficient material, patient may still proceed with protocol treatment. Archived formalin fixed paraffin embedded (FFPE) tissue should be confirmed as available for all patients. TCR sequencing will be performed on biopsy tissue or, where insufficient, archived tumor tissue. PD-L1 tumor and immune cell staining will be performed on both biopsy and archived tissue. TCR sequencing will be performed on PBMC collected at baseline. Pre-treatment research blood can be drawn anytime during screening or on Cycle 1, Day 1 prior to treatment administration.

Submission will be requested at the end of the study to allow for IHC to be performed within 60 days of slides being cut. From the time of request, sites will have 30 days to submit tissue.

f: See Section 5.3.1, Section 11.1 and Appendix B for guidance on treatment beyond progression

g: Informed consent to be obtained within 30 days prior to the start of protocol therapy.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 9 weeks (+/- 7 days). In addition to a baseline scan, confirmatory scans should also be obtained, not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer *et al*., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Treatment may be continued in cases of radiologic progression at the first 9 week (+/- 7 days) CT if all of the following criteria are satisfied (see Section 5.3.1 and Appendix B):

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesions (including up to 4 new lesions added to the sum)
- No more than 4 new lesions included in the sum.

NOTE: If treatment is continued in the case of radiologic progression at the first 9 week (+/- 7 days) CT, a reassessment scan must be performed at 4 weeks (+/- 7 days) to rule out ongoing progression.

For patients who continue treatment in the case of radiologic progression at the first 9 week (+/- 7 days) CT:

- At any subsequent CT scan patients who have stable disease as compared to the 9 week (+/- 7 days) CT scan will be allowed to continue on study treatment.
- Patients who continue treatment in the case of radiologic progression at the first 9 week (+/- 7 days) CT, and later experience a PR or CR (as compared to baseline CT) will be recorded as delayed responses.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab and/or bevacizumab.

Evaluable for objective response. All patients will be evaluable for response from the time of their first treatment with atezolizumab and/or bevacizumab. Patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at

least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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 patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, 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.

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.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans

should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. Furthermore, the PET portion of the CT introduces additional data which may bias an investigator. For this reason, PET-CT is not an option for tumor measurements in this study.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described

in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression

status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** Radiographic responses or stable disease must be confirmed 4 or greater weeks after the first scan documenting that status. In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*	'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

Investigators (or, when unavailable, a qualified representative from each institution) will meet via

teleconference every 2 weeks.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/CTMS. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) .

12.3 Collaborative Agreements Language

N/A

12.4 Genomic Data Sharing Plan

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Primary Objectives
To assess the anti-tumor activity (proportion of patients with objective response by RECIST 1.1 criteria) of atezolizumab and bevacizumab in patients with recurrent, persistent or metastatic cervical cancer.

Secondary Objectives
To estimate the duration of progression free survival (PFS) and overall survival (OS)

To assess safety by CTCAE v.5.0

Integrated Biomarker
Integrated Biomarker: To describe the efficacy of the combination of atezolizumab and bevacizumab as measured by objective response, by PD-L1 expression on tumor and immune cells measured by semi-quantitative immunohistochemistry (IHC)

Exploratory Biomarker
To describe the efficacy of the combination of atezolizumab and bevacizumab as measured by objective response, by intratumoral and peripheral TCR clonality and tumor infiltrating lymphocyte proportion

13.2 Sample Size/Accrual Rate

Primary objective:
Objective response rate (ORR, either partial or complete response) defined by RECIST v1.1 criteria.

Null hypothesis: The administration of atezolizumab with bevacizumab to patients with persistent, metastatic or recurrent cervical cancer does not yield an overall response (ORR) greater than 15 percent.

Alternative hypothesis: The administration of atezolizumab with bevacizumab to patients with persistent, metastatic or recurrent cervical cancer yields an overall response (ORR) of 40% or greater.

Statistical Considerations:
A Simon 2-stage Phase II design will be used to address the primary endpoint of ORR. The unacceptable response rate is 0.15; desirable response rate is 0.40. With an error rate of (Type I error of 0.1, Type II error of 0.1), 22 patients are needed. With 22 patients, there is a 90% power to show a difference in response rate from 15 to 40%. The trial will continue to stage two only if two or more out of 10 patients show a response in the first stage. Six or more patients out of 22 must exhibit a response for the study to be positive. The ORR (either partial or complete response) defined by RECIST v1.1 will be calculated assuming binomial proportions and a 90% confidence interval will be provided.

Early stopping rule. We will stop for safety if >=3/10 DLTs are observed or at the end of the study if >=5 DLTs out of 22 patients are seen we will deem the regimen not safe. These boundaries were calculated assuming 0.1 and 0.30 as safe and unacceptably safe rates respectively (https://www.ncbi.nlm.nih.gov/pubmed/16011702).

Definition of a Dose-Limiting Toxicity (DLT)
For the early stopping rule for safety component of this study a DLT is defined as:

Any Grade 4 immune related adverse event
Any >= grade 3 colitis
Any Grade 3 or 4 noninfectious pneumonitis (irrespective of duration)
Liver transaminase (ALT and/or AST) elevation > 8 x ULN or total bilirubin > 5 x ULN
Any >= grade 3 non immune related adverse event except for the exclusion list below
Any Grade 3 or higher fistula/leak/bowel perforation
Treatment related death

A DLT does not include:

Grade 3 fatigue
Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replace therapy
Grade 3 infusion related reaction
Grade 3 or 4 neutropenia (that is not associated with fever or infection) lasting <= 7 days
Grade 3 or 4 lymphopenia
Grade 3 thrombocytopenia that is not associated with clinically significant bleeding
Isolated grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention
Grade 3 hypertension

Accrual rate is estimated to be 4 patients/month.

13.3 Stratification Factors

N/A

13.4 Analysis of Secondary Endpoints

Progression-Free survival (PFS), defined as time from the date of start of treatment to the investigator determined date of progression (determined by RECIST v1.1 criteria), or death due to any cause, whichever occurs first. For individuals who are alive and progression free, PFS will be defined as the time from the study enrollment date to the date of the patient's last radiographic disease assessment. The expected median duration of PFS in this population is 3.5 - 4.5 months.

Overall survival (OS), defined as time from the date of start of treatment to death.

Safety endpoint: safety as measured by frequency and severity of adverse events by Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 assessed in those patients who initiate their study treatment.

Integrated biomarker: PD-L1 IHC: We will describe the efficacy of the combination of atezolizumab and bevacizumab as measured by objective response, in patients according to PD-LI expression. PD-L1 expression will be assessed following a pre-specified scoring algorithm for tumor cells and immune cells. The association of PD-L1 expression, baseline demographics and clinical outcome will be determined.

Exploratory biomarker: We will describe the efficacy of the combination of atezolizumab and bevacizumab as measured by objective response, by intratumoral and peripheral TCR clonality and tumor infiltrating lymphocyte proportion.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab and/or bevacizumab.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions will be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B EXAMPLES ON HOW TO ASSESS TUMOR RESPONSES

The methods used to assess tumor response follow to a large extent RECIST 1.1 but are modified at the first scan (performed at 9 weeks +/- 7 days) to allow for temporary inflammation of the tumors that could result from activation of an immune response system. Below are examples of hypothetical cases which can be used as a guide for evaluating your patient.

The protocol specifies continuation of treatment in cases of radiologic progression at the first 9 week (+/- 7 days) CT if all of the following criteria are satisfied:

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesion (including up to 4 new lesions added to the sum)
- No more than 4 new lesions included in the sum

NOTE: If treatment is continued in the case of radiologic progression at the first 9 week (+/- 7 days) CT, a reassessment scan must be performed at 4 weeks (+/- 7 days) to rule out ongoing progression.

For patients who continue treatment in the case of radiologic progression at the first 9 week (+/- 7 days) CT:

- At any subsequent CT scan patients who have stable disease as compared to the 9 week (+/- 7 days) CT scan will be allowed to continue on study treatment.
- Patients who continue treatment in the case of radiologic progression at the first 9 week (+/- 7 days) CT, and later experience a PR or CR (as compared to baseline CT) will be recorded as delayed responses.

Example 1

Patient obtains a baseline measurement on 12/31/2015, enrolls onto study, and starts therapy on 01/01/2016.

……

Date of Evaluation: 12/31/2015 Baseline Tumor Measurement

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm

Notes: The nadir is 10 cm. Partial response will occur if the total is ≤ 7 cm (≥ 30% or greater decrease from nadir of 10). Progression will occur if the total is > 14 cm (>40% or greater increase from nadir of 10).

……

Date of Evaluation: 3/4/2016 Nine Week Assessment

Site of Lesion Tumor Size

Site 1	6 cm
Site 2	7 cm
Total	13 cm

Time point response: **Neither progression nor response since 7cm < total < =14 cm.** Although the total ≥ 12 cm (≥ 20% or greater increase from nadir of 10), an allowance is made for this type of therapy at this time. The nadir is revised to 13 cm. The threshold for progression is now ≥ 15.6 cm (≥ 20% or greater increase from nadir of 13). Partial response can be obtained if the total is ≤ 7 cm, same as before.

……

Date of Evaluation: 5/6/2016 18 Week Assessment

Site of Lesion	Tumor Size
Site 1	8 cm
Site 2	8 cm
Total	16 cm

Time point response: **Progression** since 16 cm ≥ 15.6 cm. The **date** of **progression** is 3/4/2016, not 5/6/2016.

Example 2

Patient obtains a baseline measurement on 12/31/2015, enrolls onto study, and starts therapy on 01/01/2016.

……

Date of Evaluation: 12/31/2015 Baseline Tumor Measurement

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm

Notes: The nadir is 10 cm. Partial response will occur if the total is ≤ 7 cm (≥ 30% or greater decrease from nadir of 10). Progression will occur if the total is > 14 cm (> 40% or greater increase from nadir of
10).

……

Date of Evaluation: 3/4/2016 9 Week Assessment

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Site 3	4 cm
Total	14 cm

Time point response: **Neither progression nor response since 7 cm < total <= 14 cm**. Up to 4 additional target tumors are allowed. Nadir revised to 14 cm. The threshold for progression is revised to ≥ 16.8 cm.

……

Date of Evaluation: 5/6/2016 18 Week Assessment

Site of Lesion	Tumor Size
Site 1	4 cm
Site 2	4 cm
Site 3	3 cm
Total	11 cm

Time point response: **Neither progression nor response** since 7 cm < total < 16.8 cm. Note, the nadir is revised to 11 cm. The threshold for progression is now ≥ 13.2 cm. In order for the patient to respond, all 3 tumors must sum to ≤ 7 cm.

……

Date of Evaluation: 7/8/2016 27 Week Assessment

Site of Lesion	Tumor Size
Site 1	2 cm
Site 2	2 cm
Site 3	2 cm
Total	6 cm

Time point response: **Partial Response** since total ≤ 7 cm. The patient's response will need to be confirmed ≥ 4 weeks later with a total ≤ 7 cm. If confirmed, her date of partial response will be 7/8/2016. Note, the nadir is now 6 cm. Disease progression would occur if the total is ≥ 7.2 cm.

Example 3

Patient obtains a baseline measurement on 12/31/2015, enrolls onto study, and starts therapy on 01/01/2016.

……

Date of Evaluation: 12/31/2015 Baseline Tumor Measurement

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm

Notes: The nadir is 10 cm. Partial response will occur if the total is ≤ 7 cm (≥ 30% or greater decrease from nadir of 10). Progression will occur if the total is > 14 cm (> 40% or greater increase from nadir of 10).

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Date of Evaluation: 3/4/2016 9 Week Assessment

Site of lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm
Site of Lesion	Non-target
Site 3	Present

Time point response: **Neither progression nor response**. This patient's measurable lesions remained the same but she acquired a new non-target lesion.

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Date of Evaluation: 5/6/2016 18 Week Assessment

Site of lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm
Site of Lesion	Non-target
Site 3	Present

Time point response: **Neither progression nor response**. New lesions that appear during week 9 will be carried forward as if they were at baseline.

APPENDIX C COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.