SUMMARY OF CHANGES
Protocol

Protocol #: CITN-14, A4_v1.0
NCI Protocol #: CITN-14, A4_v1.0
Protocol Version Date: October 12, 2022

I. Changes requested by the Pharmaceutical Management Branch

#	Section	Page	Comments
1.	8 1.1	77	Revised the Atezolizumab drug information, as requested by the Pharmaceutical Management Branch on October 6, 2022.

II. Changes initiated by the Protocol Principal Investigator and CITN Coordinating Center

#	Section	Page	Comments
2.	3.2.8	25	Clarified that oral prednisone > 10 mg/day or equivalent is prohibited.
3.	3.2.14	27	Revised criterion to align with current available literature and standard language used on other immunotherapy trials. As currently written, exclusion criterion 3.2.14 is too prescriptive and limits enrollment of patients with established stability for autoimmune disease. As appropriate, allowing enrollment of these patients following consultation with the Protocol PI and/or CITN Coordinating Center may help trial accrual.

III. Administrative Changes

#	Section	Page	Comments
4.	All sections	All pages	Updated version and date throughout protocol

NCI Protocol #: CITN-14

Local Protocol #: CITN-14

ClinicalTrials.gov Identifier: *[TBD]*

TITLE: A Randomized Phase II Study of Atezolizumab (MPDL3280A) plus Recombinant Human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma

Coordinating Center: Cancer Immunotherapy Trials Network (CITN), Fred Hutchinson Cancer Research Center

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Responsible Data Manager: N/A

NCI-Supplied Agent(s): Atezolizumab (MPDL3280A; NSC 783608)
Recombinant Human IL-7 (CYT107; NSC 767713)

Other Agent(s): N/A

IND #: [redacted]

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Amendment #4 / Version 1.0 / October 12, 2022

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at https://www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email:1-888-823-5923 ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (*i.e.*, patient eligibility or treatment-related) Contact the CITN Central Operations and Statistical Center at citn@fredhutch.org or (514) 718-2858		
For nonclinical questions (*i.e.*, unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

STUDY SUMMARY

Abbreviated Title	Urothelial Carcinoma Therapy with Atezolizumab plus CYT107
Trial Phase	Phase II
Clinical Indication	Locally advanced or metastatic urothelial carcinoma
Trial Type	Randomized, controlled trial with initial Safety Run-In phase
Safety Run-In	Enrollment of 6 patients to the Experimental arm. If acceptable safety profile, patient randomization will begin.
Type of control	Randomized trial with primary end point of objective response rate (ORR). Secondary endpoint of clinical benefit rate (CBR), progression-free survival (PFS), Duration of Response (DOR) and overall survival (OS) will compare the control arm to the experimental arm.
Randomization arm *1 – Experimental* *2 – Control*	 IL-7 (CYT107), 10 mcg/kg intramuscularly (IM) days 1, 8, 15 and 22 of cycle 1 only (28-day cycle) + Atezolizumab, 1200 mg intravenously (IV) day 8 of cycle 1 (28-day cycle) and day 1 of subsequent cycles (21-day cycle) Atezolizumab, 1200 mg intravenously (IV) day 1 of each cycle (21-day cycle)
Stratification Factor	None
Trial Blinding	None
Number of trial patients	54 patients
Estimated duration of trial	Trial is expected to be completed over a period of 30 months.
Duration of Participation	Each patient will participate in the trial from the time the Informed Consent Form (ICF) is signed through final protocol-specified contact. The active study will end when the last patient reaches 2 years.

TABLE OF CONTENTS

1. OBJECTIVES

The goals of this trial are to evaluate the safety and tolerability of the investigational treatment combination, and to determine whether the addition of CYT107 to atezolizumab improves the objective response rate achieved by atezolizumab alone in patients with advanced/non-resectable bladder cancer who have recurrent disease after platinum chemotherapy.

1.1 Primary Objectives

To determine the clinical efficacy of the investigational treatment combination.

The primary endpoint will be the Objective Response Rate (ORR), defined by Complete Response (CR) or Partial Response (PR) as measured by RECIST v1.1.

1.2 Secondary Objectives

To determine the clinical activity and toxicity of the investigational treatment combination.

1.2.1 The clinical benefit rate (CBR), progression-free survival (PFS), duration of response (DOR), as measured by RECIST 1.1 and irRC, and overall survival (OS).

1.2.2 The CBR, PFS, DOR, and OS in all patients and patients stratified by PD-L1 expression levels in the tumor microenvironment.

1.2.3 The safety and toxicity of addition of CYT107 to atezolizumab.

1.3 Exploratory Objectives

To determine the immune correlates of the clinical activity of the investigational treatment combination.

The endpoints will include the evaluation of the effect of the investigational treatment combination on the tumor microenvironment, based upon baseline and post-baseline tumor biopsy comparisons of:

- Number, distribution, and phenotype of tumor-infiltrating cells
- PD-L1 expression
- Expression of Interferon γ (IFNγ) and associated inflammatory gene expression in the tumor microenvironment

Explore the effect of the investigational treatment combination on the number and phenotype of tumor-specific T cells in the peripheral blood. Investigate for evidence that the investigational treatment combination increases the exposure of bladder cancer-specific antigens (*e.g.,* Cancer/Testis Antigens or neoantigens). Investigate changes in tumor microenvironment that correlate with response or provide information on potential actionable causes for lack of clinical benefit. Investigate the potential that administration of atezolizumab with CYT107 may perturb the pharmacokinetics and immunogenicity of CYT107.

2. BACKGROUND

2.1 Study Disease(s)

The proposed clinical trial is a phase II, open-label, multicenter, randomized study of the administration of Atezolizumab (MPDL3280A) monotherapy or in combination with Recombinant Human IL-7 (CYT107) in patients with advanced or metastatic urothelial carcinoma.

Urothelial carcinoma is the fifth most common malignancy in the United States [Siegel 2014]. Advanced or metastatic urothelial carcinoma carries a grim prognosis and has limited treatment options [von der Maase 2000]. The immunogenicity of urothelial bladder cancer (UBC) was first demonstrated by the successful use of BCG for non-muscle invasive bladder cancer and carcinoma in situ [Kamat 2001]. More recently, antibodies blocking PD-1/PD-L1 signaling in endogenous T cells have induced dramatic and durable clinical responses in patients with metastatic urothelial carcinoma, further highlighting urothelial carcinoma as a compelling target for T-cell immunotherapy [Powles 2014; Plimack 2017]

Early studies with impressive response rates and durable responses led to regulatory approval of 5 different PD-1/PD-L1 antibodies. This includes atezolizumab, durvalumab, nivolumab, avelumab, and pembrolizumab. Survival outcomes have been assessed in randomized phase 3 trials with atezolizumab and pembrolizumab. Pembrolizumab was successful in demonstrating improved overall survival outcomes over taxane or vinflunine chemotherapy in the post-platinum–treated advanced or metastatic UBC setting [Bellmunt 2017]. Atezolizumab also demonstrated an overall survival benefit over taxane or vinflunine chemotherapy in the post-platinum–treated advanced or metastatic UBC setting in the intention to treat analysis (presentation abstract). However, the primary study endpoint was based on an enrichment biomarker approach based on PD-L1 immunohistochemical staining, and that enrichment approach failed, as the biomarker was very clearly prognostic for improved outcomes in both arms, but not predictive for improved response to atezolizumab.

We now attempt to demonstrate improved clinically meaningful outcomes with the addition of CYT107 to atezolizumab over atezolizumab alone for patients with advanced or metastatic urothelial carcinoma.

2.2 CTEP IND Agent(s)

2.2.1 Atezolizumab (MPDL3280A)

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of 2 heavy chains (448 amino acids) and 2 light chains (214 amino acids) and is produced in Chinese hamster ovary cells [Investigators's Brochure]. 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 nonglycosylated antibody that has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits the interaction with its

PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.

Atezolizumab shows antitumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab was approved in the United States by the FDA in 2016 for the treatment of locally advanced or metastatic urothelial carcinoma and as well as metastatic non–small cell lung carcinoma. In March 2021, following the review of recent Atezolizumab bladder cancer studies and evaluation of other available treatment options, the indication for Atezolizumab in patients with urothelial carcinoma who have previously received platinum-based chemotherapy has been withdrawn in the United States, according to the drug's developer, Roche. The decision to withdraw the agent for use in this patient population does not affect indications for Atezolizumab in other diseases including non-small cell lung cancer, small cell lung cancer, metastatic triple-negative breast cancer, hepatocellular carcinoma and melanoma or as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma.

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 2006; Hamanishi 2007; Okazaki 2007; Hino 2010]. PD-L1 binds to 2 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 2005; Keir 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 antitumor immunity, resulting in immune evasion [Blank 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.

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 2002; Strome 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 (irAEs) reported from the 2 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*

A summary of clinical data from company-sponsored atezolizumab trials is presented below. Details of all ongoing studies can be found in the most recent 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 [Investigators's Brochure]. Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21−89 years), body weight, gender, positive ATA status, albumin levels, tumor burden, region, or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status. No formal PK drug-drug interaction studies have been conducted with atezolizumab, and the interaction potential is unknown. Further details can be found in the current Investigator's Brochure.

The development of antitherapeutic 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) [Investigators's Brochure]. Patients dosed at ≥10 mg/kg maintained C_{min} values well above the target serum concentration of 6 mcg/mL despite the detection of ATAs. Accordingly, the development of detectable ATAs does not appear to have a clinically significant impact on PK for doses above 10 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 May 10, 2016, atezolizumab has been administered (alone or in combination with other agents) to approximately 6053 patients with solid tumors and hematologic malignancies [Investigators's Brochure]. The first-in-human monotherapy study PCD4989g (in patients with locally advanced or metastatic

solid tumors or hematologic malignancies) provides the majority of monotherapy safety data, with 629 safety-evaluable patients as of the data extraction date. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of AEs have been determined.

Fatigue, decreased appetite, nausea, diarrhea, constipation, and cough were commonly reported AEs in single and combination therapy [Investigators's Brochure]. AE profiles are similar across tumor types studied, including non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma, and are consistent with the mechanism of action of atezolizumab. The overall immune-mediated AEs reported were considered moderate in severity, and the majority of patients were able to continue on atezolizumab therapy.

As of the data extraction date of December 15, 2015, there were 629 safety-evaluable patients from the first-in-human phase 1a study PCD4989g [Investigators's Brochure]. The median age was 61 years. Of the 629 patients, 619 patients (98.4%) reported at least one AE of any grade or attribution to atezolizumab, and 316 patients (50.2%) experienced at least one grade 3 or 4 AE of any attribution. A total of 444 patients (70.6%) reported at least one treatment-related AE, and 86 patients (13.7%) experienced at least one treatment-related grade 3 or 4 AE. The most frequently observed AEs of any grade and attribution (occurring in ≥10% of treated patients) include fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema, and dizziness.

Serious AEs (SAEs) have been reported in 261 patients (41.5%) in study PCD4989g [Investigators's Brochure]. Reported SAEs were consistent with the underlying disease. Treatment-related SAEs (57 patients [9.1%]) included pyrexia, dyspnea, pneumonitis, malaise, fatigue, hypoxia, colitis, and bone pain. Pooled single-agent safety data from 1978 patients with UC, NSCLC, and other indications (including trial PCD4989g) indicate that the most frequent (>1% of patients) serious adverse drug reactions (regardless of grade) include dyspnea (3.0%), back pain (1.2%), and abdominal pain (1.1%). A list of AEs considered "expected" for atezolizumab is presented in Section 7.1.1.1.

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 [Investigators's Brochure]. 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, nephritis, myocarditis, and meningoencephalitis.

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 NSCLC, RCC, and UC [Investigators's Brochure]. Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UC, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Both the preliminary and more mature efficacy data available suggest that treatment with atezolizumab as a single agent or in combination with other therapeutic agents results in antitumor activity across a range of tumor types and hematologic malignancies (UC, NSCLC, RCC, TNBC, melanoma, CRC, and NHL) and across lines of therapy. Clinical benefit was observed in terms of objective responses, durability of responses, and overall survival. Improved efficacy of atezolizumab was observed in the unselected patient population, as well as in patients with higher PD-L1 expression on TCs or ICs (*e.g.,* NSCLC) or on ICs only (*e.g.,* mUC, RCC).

2.2.2 Recombinant Glycosylated Human Interleukin-7 (CYT107)

A relatively nontoxic regimen of weekly IL-7 will substantially increase the total body complement of T cells of all phenotypes. The current trial will test whether addition of IL-7 to atezolizumab, using an IL-7 regimen known to increase the total body complement of T cells, will increase the frequency and depth of clinical responses to atezolizumab.

2.2.2.1 *Mechanism of action*

IL-7 is a homeostatic growth factor for T cells that normally contributes to maintaining the normal number of peripheral blood T cells. IL-7 is the T-cell equivalent of erythropoietin and thymopoietin with multiple functions that could increase the efficacy of atezolizumab. IL-7–mediated signaling can induce proliferation in the absence of T-cell receptor signaling [Swainson 2007]. IL-7 signals through the IL-7 receptor (IL-7R) heterodimer composed of the common γ-chain (CD132) cytokine receptor and a unique IL-7Rα (CD127). During normal conditions, IL-7R expression is maintained on resting T cells [Mackall 2011] and endogenous IL-7 is continuously available in secondary lymphoid organs as a result of stromal cell IL-7 production [Takada 2009].

2.2.2.2 *Summary of Nonclinical Experience*

Exogenous IL-7 induces expansion of most categories of T cells. In preclinical and clinical studies IL-7 has been shown to:

1. Increase peripheral blood T cells by several fold with little toxicity [Levy 2009; Sportes 2010; Perales 2012; Tredan 2015; Sheikh 2016],
2. Expand all categories of T cells including CD8, CD4 and memory T cells [Sportes 2010],
3. Increase the total body complement of T cells including increased size of lymph nodes, spleen, liver [Sportes 2008],

4. Increase T-cell receptor (TCR) diversity by preferentially stimulating the growth of TREC positive, naïve T cells [Sportes 2008]. Continuous signaling by IL-7 induces antiapoptotic and costimulatory responses that are essential for the survival of naïve T cells.
5. Maintain effector T-cell function,
6. Increase the ratio of CD8+ T cells to Tregs, as IL-7Rα expression is relatively low on FOXP3+ Treg cells compared with nonregulatory T-cell subsets [Liu 2006; Seddiki 2006].
7. Increase tissue infiltration of T cells into gut mucosa (other tissues have not been examined) [Sereti 2012].
8. Reverse neutrophil lymphocyte ratios [unpublished data – CITN12-03 (NCT01881867)]
9. Augment vaccine-induced cell responses in murine models [Melchionda 2005]
10. Augment immune-mediated control of both tumors and viruses [Mackall 2011].

After either T-cell activation, IL-7 signaling, or both, IL-7Rα is down-regulated on terminally differentiated, senescent T cells [Fry 2003], [Park 2004] but becomes reexpressed after several days and remains expressed during the later contraction phase. IL-7Rα is also selectively expressed on a small minority of effector T cells that are destined to enter the central memory T-cell pool, thus implicating IL-7 as a modulator of the effector to memory cell transition [Kaech 2003].

2.2.2.3 *Summary of Clinical Experience*

The CYT107 dose and regimen have been established in prior clinical trials. More than 380 patients have been exposed to CYT107. Weekly CYT107 × 3 or 4 at doses of 10 to 20 µg/kg can double the number of peripheral blood T cells (CITN Immune Monitoring Lab data). Both naïve and memory T cells are expanded by CYT107 with a peak of proliferation at day 7. Repeated doses of CYT107 induce expansion of CD4+ and CD8+ T cells subsets. Importantly, there is no significant difference between the 10 and 20 mcg/kg dose levels and biological effect on CD4+ and CD8+ T-cell number increases [Levy 2012], Figures 1A and 1B]. The increases last for weeks to months in some individuals [Levy 2009]. Extrapolating from the increase in size of lymph nodes, spleen, and liver with FDG-PET, the total body burden of T cells also increased correspondingly [Sportes 2008]. However, the 10 µg/kg dose level is tolerated better, with no reported serious unexpected serious adverse reactions (SUSARs) reported compared to 4 cases reported at the 20 µg/kg dose. Importantly, the 20 µg/kg dose level has been associated with autoimmune adverse events, include Henoch-Schonlein purpura, lichen planus and the emergence of neutralizing antibodies [CYT107 Investigator's Brochure].

Regimens of weekly IL-7 at the 10 µg/kg level demonstrate an acceptable safety profile with very few grade 3 or 4 adverse events. More than 380 patients have been exposed to CYT107, including 236 patients in 7 phase I/IIa dose escalation studies with CYT107 in oncology, hematopoietic stem cell transplantation (HSCT), human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) infected patients and 2 phase II studies in patients with HIV. CYT107 has been well tolerated [CYT107 Investigator's Brochure]. The most frequent adverse events are:

injection site reactions, lymphadenopathy, pyrexia, rash, and fatigue. A cumulative 819 administrations of CYT107 triggered 555 injection site reactions AE, *i.e.,* 70% of CYT107 administrations led to at least one injection site reaction. The worst grade reported was grade 2 in 159 of 819 administrations (19.4%). No grade 3 or 4 injection site reactions were reported.

Among the 555 injection site reactions related to CYT107:

- 113 (20.3%) were of grade <1
- 283 (51.0%) were of grade 1
- 159 (28.7%) were of grade 2
- No grade 3 or 4 injection site reactions were reported.

Of note, this scoring was performed with reference to the DAIDS 2.0 scale which is more severe than CTCAE scoring.

One true anaphylactic reaction and 4 acute allergic reactions have been reported, strictly in studies with repeated cycles of CYT107. The immunogenicity frequency and the occurrence of NADA (neutralizing antibodies) are higher with the exposure to multiple cycles of CYT107.

Two studies analyzed the pharmacokinetics of CYT107 in patients with HIV-1 with CD4 T-cell counts of 101-400 cells/µL and plasma HIV RNA <50 copies/mL while receiving highly active antiretroviral therapy (HAART) for ≥12 months. Three dose levels of CYT107 were tested sequentially: 10, 20 and 30µg/kg. Increasing doses induced a dose response increase in peripheral blood T cells. The increases were nonlinearity above 20µg/kg/week in the lymphopenic patients and above 30/µg/kg/week for the non-lymphopenic patients. The nonlinearity was presumed to be to the administered IL-7 being cleared by binding to an increased number of T cells, *i.e.,* a "Target Mediated Drug Disposition" [CYT107 Investigator's Brochure].

Up to June 2013, all preclinical and clinical studies were conducted by Cytheris S.A. In September 2013 all CYT107 related assets were transferred to RevImmune, the company now responsible for conducting CYT107 development.

The CITN has one ongoing trial of CYT107 started with Cytheris and continued with RevImmune CITN is the IND sponsor. The trial is testing CYT107 in patients with metastatic castration-resistant prostate cancer after treatment with sipuleucel-T (PROVENGE®, Dendreon Corporation), a prostatic acid phosphatase vaccine. The goal is to determine whether treatment with CYT107 can substantially increase and prolong immune responses to prostatic acid phosphatase and thereby eventually provide a novel, nontoxic regimen to prolong the survival of patients with metastatic castration-resistant prostate cancer [CITN12-03 (ClinicalTrials.gov Identifier: NCT01881867)].

After therapy with standard sipuleucel-T, patients are randomly assigned to observation or administration of CYT107 10 µg/kg on days 0, 7, 14, and 21. The randomized trial has accrued 54 of 70 patients with half in the CYT107 arm. Results

to date have confirmed that CYT107 (1) increases peripheral blood CD8+ and CD4+ T cells, and (2) reverses the neutrophil to lymphocyte ratio. Of note, a high neutrophil to lymphocyte ratio is a poor prognostic sign in most, if not all, clinical cancer circumstances in which it's been assessed [Templeton 2014] including bladder cancer [Bhindi 2016]. No DLT have been observed.

2.3 Other Agent(s): N/A

2.4 Rationale

Very few preclinical studies have combined IL-7 with PD-1 or anti-PD-L1 checkpoint blockade. One murine study showed the therapeutic efficacy of concomitant blockade of CTLA-4 and PD-1 relies on interdependence of IL-7 and IFN-γ signaling in T cells, predicting the exogenous IL-7 will boost the therapeutic efficacy [Shi 2016]. Another study of murine sepsis showed that IL-7 reverses immune suppression by increasing lymphocyte proliferation, expression of lymphocyte adhesion molecules, interferon-gamma production, and CD28 expression on splenic CD8+ T cells. Combined treatment with IL-7 and anti-PD-1 produced additive effects on CD28 expression, lymphocyte proliferation, and splenic secretion of interferon-gamma [Shindo 2015]. Of note, CYT107 therapy is currently being tested in human sepsis [ClinicalTrials.gov Identifier: NCT02640807]. In a recent Science paper [Pauken 2016] using the mouse model of chronic lymphocytic choriomeningitis virus (LCMV) infection explored the combined effect of IL-7 and anti-PD-L1 on the development and functionality of exhausted T cells. They confirmed that treatment with IL-7 starting in the effector phase can prevent development of T-cell exhaustion. By 8 to 11 weeks after treatment, however, the anti-PD-L1 reinvigoration of T cells was lost, and the quantity, proliferation, effector function, and inhibitory receptor expression of LCMV-specific CD8 T cells in the anti-PD-L1–treated mice were comparable to those in control-treated mice. Interestingly at this stage the combined treatment with IL-7 and anti-PD-L1, resulted in more antigen-specific CD8 T cells and improved coproduction of interferon-γ and tumor necrosis factor–α.

Atezolizumab induces remarkable responses in a subset of patients, yet the percentage of complete responses in the "all comers" population was only 5.5% and the median OS for all patients was only 7.9 months [Package Insert 2017]. Various mechanisms of immune escape, including (1) the lack of strong, tumor-specific antigens or epitopes recognized by T cells, (2) impaired or suppressed antigen presentation machinery including downregulation of major histocompatibility complex on cancer cells, (3) impaired or suppressed cytotoxic T-cell activation, (4) poor infiltration of T cells into the tumor microenvironment, and (5) increased immunosuppressive cytokines and cells in the tumor microenvironment prevent a large proportion of cancer patients from driving clinical benefit from anti-PD1/PD-L1 therapies [Kim 2016]. Thus, additional therapies to increase the frequency and depth of responses to atezolizumab are needed.

Atezolizumab has induced phenomenal lifesaving responses in some patients with advanced urothelial carcinoma, presenting an incredible foundation for building more effective regimens. The current trial will determine whether, by increasing the total body complement of T cells and expanding the T-cell repertoire, the addition of CYT107 to atezolizumab will improve upon the clinical benefit provided by atezolizumab alone.

2.5 Integrated Correlative Studies Background

2.5.1 *Evaluation of peripheral CD4+ and CD8+ T-cell counts – Integrated Laboratory Correlative Study #1*

As described above, CYT107 has been shown to double the number of peripheral blood lymphocytes including T cells. Thus, CD4+ and CD8+ T-cell numbers are important biomarkers for the effect of CYT107 on the peripheral T-cell populations. To assess the overall pharmacodynamic effect of atezolizumab plus CYT107 and to determine whether CYT107 in combination with atezolizumab results in the same, or different level, of expansion of peripheral lymphocytes, T-cell counts (both CD4+ and CD8+) will be evaluated in CLIA certified laboratories locally at each site. CD4+ and CD8+ T-cell counts will be evaluated at baseline, during treatment, and at end of therapy.

Hypothesis: The combination of atezolizumab with CYT107 will result in similar levels of peripheral blood T-cell expansion as with CYT107 alone.

2.5.2 *Slide-Based Immune Phenotype Panel -- Multispectral IHC – Integrated Laboratory Correlative Study #2*

Because tumor-infiltrating immune cells are associated with clinical outcomes, infiltrates from pre-treatment tumor tissue and from biopsies taken during treatment will be assessed by IHC to determine extent and the nature of T-cell infiltration and of the overall immune milieu of the tumor microenvironment (TME).

Paired baseline and post-baseline tumor biopsies will be evaluated using quantitative multicolor immunohistochemistry (IHC) with Perkin-Elmer's Vectra IHC platform. This platform employs spectral deconvolution imaging to separate optical signals from each antibody together with state-of–the-art image analysis capabilities to facilitate robust quantitative slide-based immunophenotyping. Using the Vectra multispectral imaging platform (PerkinElmer), adjacent tumor sections will be stained and imaged with a series of 5-6 antibodies per section simultaneously to investigate the spatial relationship between key immunomodulatory cell types and molecules. The antibodies will include, but are not limited to, the following: pancytokeratin (AE1/AE3), CD8, CD4, PD-1, PD-L1, CD68, CD163, FOXP3, arginase, and pan-MHC class I and class II. Data will be generated in the form of total positive cells, positive cells/mm2, percentage positive cells in a population, ratios of cells and molecules of interest (*e.g.,* PD-L1:CD8 or FOXP3+CD4+:CD8). Additionally, tumors may also be assayed by IHC for a variety of other markers including CD80, IFN-gamma CD3, CD5, TIA-1, CD20, CD11b, CD137, CD45RO, CD301CD56 and CD16 (natural killer [NK] and NK T cells), CD79a (B cells), GITR, TIM-3, FOXP3, LAG3. Furthermore, quantitative analysis of tumor-infiltrating lymphocyte (TIL) distribution (*i.e.,* stromal, and interface/invasive margin) will be performed. Anti-PD-L1 immunohistochemical staining will be performed at HistoGeneX (Naperville, IL) with the SP142 clone, in addition to the multispectral IHC (msIHC) to serve as both an independent test and control for the reproducibility of the msIHC assay. The study is intended to evaluate for changes in the immune profile of the tumor microenvironment. If sufficient archival tumor tissue collected before therapy is not

available, a baseline biopsy will be obtained before enrolling in the study as part of this protocol.

IHC studies will be performed under the direction of Dr. [redacted] at the Fred Hutchinson Cancer Research Center (Fred Hutch) Experimental Histopathology Laboratory, Seattle, WA, or other agreed upon investigator.

***Hypothesis**:* The combination of atezolizumab with CYT107 will alter the TME (tumor microenvironment) towards a pro inflammatory phenotype.

2.5.3 *Assessment of tumor biopsy by gene expression analysis -- Interferon γ (INFγ) Gene Expression Signature - NanoString® nCounter® Human Immunology V2 Panel and the nCounter® PanCancer Immune Profiling Panel – Integrated Laboratory Correlative Study #3*

To identify potential signatures correlating with tumor T-cell infiltration patterns and clinical response Tumor tissue will be tested for gene expression using NanoString® technology on unstained tissue formalin-fixed paraffin-embedded (FFPE) slide material. Specifically, slides will be analyzed using both a 770-gene panel (nCounter® PanCancer Immune Profiling Panel) which contains markers for 24 different immune cell types and populations, 30 common cancer antigens and genes that representing immune responses including checkpoint blockade genes as well as the NanoString® nCounter® Human Immunology V2 Panel which contain genes associated with the INFγ Gene Expression Signature. These gene expression profiles may provide an additional detailed phenotype to guide correlative investigation.

NanoString®-based gene expression analysis, specifically for the IFN γ Signature, will be used to test the hypothesis that the investigational study treatment regimen, CYT107 plus atezolizumab, will promote a proinflammatory antitumor immune response. The IFNγ Signature, which is comprised of IDO1, CXCL10, CXCL9, HLA-DRA, STAT1 and IFNγ, has previously been shown to correlate with anti-PD1 response and nonresponse. RNA will be extracted from all paraffin-embedded tumor samples and analyzed using the NanoString® nCounter Immunology V2 Profiling Pane, which includes the aforementioned genes of the IFNγ Signature, as well as over 700 other genes associated with inflammation. The samples used will be taken from tissue sections adjacent to those stained for multispectral IHC to facilitate comparison between these analysis sets. Samples will consist of matched pre- and post-treatment FFPE biopsies.

These analyses will be performed in coordination with NanoString® Technologies in Seattle, WA, and analyzed using qualified analytic tools at the immunopathology lab of the Fred Hutch.

***Hypotheses**:* The combination of Atezolizumab with CYT107 will alter the TME towards a pro inflammatory GEP phenotype, and distinct gene expression patterns will be identified that may correlate with clinical outcomes.

2.5.4 *T-Cell Receptor Repertoire Analysis -- TCR sequencing – Integrated Laboratory Correlative Study #4*

We will perform TCR sequencing where pretreatment and post-treatment biopsies are available. TCR repertoire analysis will be performed on RNA extracted from FFPE biopsies, and T cells isolated from PBMCs from the research blood collections throughout study participation. TCR repertoire analysis has been standardized and commercialized by Adaptive Biosciences. The TCR sequences will also specifically be queried for sequences already known to encode for TCRs reactive to shared antigens often expressed in urothelial transitional cell carcinoma (*e.g.,* MAGE-A3, NY-ESO-1, LAGE-1, and PRAME).

Samples will be analyzed at Adaptive Bioscience in Seattle, WA, or other agreed upon vendor or collaborator.

Hypothesis*:* The combination of Atezolizumab with CYT107 will result in emergence and/or increased prevalence of specific TCR sequences reflecting the clonal expansion of antitumor T cells, and expansion of those specific T-cell clones in TILs (exhibited by higher TCR clonality) will be associated with improved response to therapy.

2.5.5 *Tumor-Associated Neo-antigen discovery -- Whole Exome Sequencing and RNAseq and Antigen Prediction – Integrated Laboratory Correlative Study #5*

In order to investigate the role of T-cell–mediated immunity directed towards tumor-specific mutant antigens, genomic sequencing and RNAseq of tumor cells from baseline tumor biopsy relative to non-tumor cells from whole blood (PBMC) will be performed to: i) identify tumor-associated neoantigens; and ii) identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities.

DNA and RNA will be extracted from baseline or archival FFPE tumor biopsies will be sequenced to identify overexpressed known “shared” tumor-associated antigens (TAAs) and nonsynonymous expressed mutations using available and standard-of-practice technologies. For example, a computational approach (BIMAS and SYFPEITHI algorithms) can be utilized to analyze and prioritize these mutation-derived “virtual” antigens in terms of their likelihood to bind to/be presented by MHC I alleles (HLA-A2, A3, A24). Potential antigens can be encoded in tandem minigene constructs with intervening P2A viral sequences to allow for equimolar expression of multiple “long” (~27 amino acids) peptides centered on the putative antigenic mutational sites. These neoantigenic libraries will be cloned into an appropriate expression vectors to allow for in vitro- transcription of neoantigen-encoding mRNA for use in ELISPOT assays to detect neoantigen immune responses. RNAseq will also identify whether common “shared” antigens are also expressed, including MAGE-A3, NY-ESO-1, LAGE-1, and PRAME. Common epitopes sequences from these shared antigens will also be transduced as above. Quantitation of mutation burden may also be important for urothelial carcinoma, where

immunogenicity and/or responses to PD-1/PD-L1 axis-directed therapies may be associated with a high mutation burden.

These analyses will be performed using qualified analytes and analytic tools at the immunopathology lab at the Fred Hutch or at a vendor, to be determined.

***Hypothesis**:* Clinical outcomes will correlate with neoantigen and mutational burden.

2.5.6 *Antitumor Immune T-cell Responses – ELISPOT – Integrated Laboratory Correlative Study #6*

If there are positive clinical responses, antigen-specific T-cell responses may be assessed by IFNγ enzyme-linked immunospot (ELISPOT) assay to provide information regarding the effect of the atezolizumab and CYT107 regimen on antigen-specific T-cell–functional antitumor responses. The ability of the investigational treatment to induce a tumor antigen-specific immune response will be assessed using ex vivo incubation of PBMC-derived T cells with autologous PBMC either pulsed with peptide antigens or recombinant proteins representing known ongoing and nascent antitumor responses (PRAME, NY-ESO-1, MAGE-A3 and/or p53), or neoantigens described above. Memory viral responses (influenza A, CEF) will also be assessed as controls. We will quantitate the strength of the antigen-specific T-cell responses and compare baseline and post-baseline T-cell responses for each putative antigen. The absolute change in ELISPOT responses for antigens will be compared between the SFC/million PBMC at baseline (before treatment initiation) and at designated time points post-treatment.

Assays will be performed in the CITN Immune Monitory Laboratory (CIML) at the Fred Hutch under the direction of Dr. [redacted], or an agreed upon vendor or collaborator.

***Hypothesis**:* The combination of atezolizumab with CYT107 will result in increased T-cell responses to known and/or neoantigens.

2.6 Exploratory/Ancillary Correlative Studies

2.6.1 *Assessment of PD-L1 expression at Baseline and Post-treatment -- Immunohistochemistry (IHC) – Exploratory Laboratory Correlative Study #1*

PD-L1 has been identified as an important correlative biomarker for clinical response to anti-PD-L1 and anti-PD-1 therapies. In particular, given that the function of atezolizumab is to block binding of PD-1 to PD-L1, expression of PD-L1 will be quantitated by IHC in baseline formalin-fixed paraffin-embedded tumor specimens, and from biopsies obtained after treatment. This is an important part of the correlative studies to explore whether this marker which correlates with response in other circumstances also correlates with response in this protocol population. For baseline samples, formalin-fixed, paraffin-embedded tissue block(s) from tumor obtained before treatment will be obtained by the clinical site either from archival samples obtained from the relevant pathology laboratories where they were processed and stored, or from baseline biopsy as part of this

protocol (core, punch, or excisional). Post-treatment, formalin-fixed paraffin-embedded tumor specimens will be obtained from biopsy at week 11 (core, punch, or excisional) as part of this protocol.

PD-L1 expression will be tested by IHC at HistoGeneX (Naperville, IL)with the PD-L1 SP142 clone assay, or at other agreed upon vendor.

Hypothesis: PD-L1 expression at baseline will correlate with clinical responses to atezolizumab and atezolizumab in combination with CYT107. In addition, atezolizumab administration may alter PD-L1 expression to an unknown extent.

2.6.2 *Evaluation of the effect of atezolizumab with and without CYT107 on circulating Lymphocyte and Monocyte numbers and Phenotype – Exploratory Laboratory Correlative Study #2*

We will assess the effects of the atezolizumab with and without CYT107 on the frequency and phenotypic character of PBMC subsets including dendritic cells (DCs), monocyte populations, T cells, NK cells, and B cells. The effect on these immune cell subtypes of checkpoint inhibitors, and other immune modulators is being investigated in other CITN trials and may provide important correlative information on the success or failure of combination immunotherapy.

A 14-color whole blood immunophenotyping assay will quantify in one panel the absolute number and proportion of T cells (both CD8+ and CD4+), NK cells (CD56+CD3-), NKT cells (CD56+CD3+), B cells (CD19+/CD20+), monocytes (CD16+), neutrophils (CD15+), as well as both myeloid DCs (CD45+HLA-DR+CD11c+CD123-) and plasmacytoid DCs (CD45+HLA-DR+CD11c-CD123+). In addition, myeloid-derived suppressor cells (MDSC) will be measured using antibodies to HLA-DR, CD11b, and CD33 in this same multiparameter flow cytometric assay. Multiparameter flow cytometry on whole blood with a 12-color panel may also be used in parallel to further define the phenotype of T cells and to identify activated T cells, T-cell subsets (including regulatory T cells). This validated panel includes the markers CD45, CD3, CD4, CD8, CD45RA, CD197 (CCR7), CD28, CD127, CD25, HLA-DR, CD279 (PD-1), CD278.

Assays will be performed under the direction of Dr. [redacted] in the CIML at the Fred Hutch.

Hypothesis: The combination of atezolizumab with CYT107 will perturb circulating lymphocyte and monocyte numbers and phenotypes to a yet unknown extent.

2.6.3 *Multiplex Cytokines -- Multiplex ELISA – Exploratory Laboratory Correlative Study #3*

Perturbations in cytokines, chemokines, and growth factors have been associated with cancers and changes in plasma cytokine concentrations of proinflammatory and immunosuppressive cytokines may correlate with clinical responses to therapy. Measureable changes in serum and plasma cytokines have been associated with checkpoint blockade therapies. Comparison of baseline plasma cytokines, chemokines

and growth factors to longitudinal measurements during therapy may improve our understanding of the immunologic effects of the combination of atezolizumab plus CYT107 on cancer. Furthermore, these assays will be used to explore whether reactive changes in cytokine levels correlates with toxicity and/or efficacy of atezolizumab and CYT107. Longitudinally collected plasma samples will be evaluated using commercial multiplex immunoassays that are quantified by immunochemiluminescence detection or other appropriate technology.

Assays will be performed at the Fred Hutch Shared Resources, or at other agreed upon vendor.

Hypothesis: The combination of atezolizumab with CYT107 will perturb cytokines, chemokines, and growth factors to a yet unknown extent.

2.6.4 *Kynurenine and tryptophan (Kyn/Trp) ratios and plasma Arginine levels – Exploratory Laboratory Correlative Study #4*

Over expression of indoleamine 2,3-dioxygenase (IDO) is known to result in increases in the Kyn/Trp ratio in blood and within some tumor microenvironments. Increases in Kyn/Trp ratios result in the subsequent suppression of T-cell responses and is a major mechanism of immune control. IDO is expressed by some tumors, but probably more importantly, it is expressed by lymphocytes as a normal mechanism and important mechanism to dampen immune responses. Expression of IDO (with subsequent increased Kyn/Trp ratio) may be one likely mechanism of checkpoint blockade and other immunotherapy failures. Thus, we will measure Kyn/Trp ratios in plasma taken at baseline, during treatment, and at end of treatment in this protocol to analyze, in patients who have failed clinical response to Atezolizumab plus IL-7 treatment, failure may be associated with increased Kyn/Trp levels.

In addition, another important mechanism of immune control and suppression is through the changing concentrations of arginine insofar as decreased levels of arginine in plasma (ie arginine depletion) is associated with decreases in CD4 and CD8 T-cell proliferation and Th1 functions. Arginine depletion can occur by the release by MDSCs of arginase which converts L-arginine to ornithine. This may be another mechanism of tumor evasion as myeloid suppressor cells with high arginase activity are found in tumors. Thus, we will also measure arginine levels in the same plasma samples taken at baseline, during treatment, and at end of treatment in this protocol to analyze, in patients who have failed clinical response to Atezolizumab plus IL-7 treatment, whether failure may be associated with increased arginine levels in plasma.

All assays will be performed at an agreed upon collaborator or vendor to be determined. .

Hypothesis*:* Failure to respond to atezolizumab plus CYT107 treatment may be associated with increased Kyn/Trp ratios and/or increased plasma arginine levels in some patients.

2.6.5 *Microbiome Analyses – Exploratory Laboratory Correlative Study #5*

Recent reports in preclinical mouse tumor models suggest that the gut microbiome has an effect on response to checkpoint blockade immunotherapy, and there is growing evidence that the intestinal microbiome may have major influences on antitumor immune responses. The microbiota has long been known to have profound effects on innate and adaptive immunity. However, the impact and importance of the gut microbiome in human cancer patients' responses to immunotherapy has not yet been well-characterized and will be important to determine. To begin to understand the role of the microbiome in responses to immunotherapy in this protocol, we will collect microbiome samples from patients at baseline and perform taxonomic profiling via 16 S rRNA gene sequencing and metagenomic whole-genome shotgun (WGS) sequencing. Fecal samples will be collected and stored using standard, at home stool-collection procedures, and we will assess the landscape of the gut microbiome. Sequencing data will be analyzed and compared to clinical responses to determine whether response or nonresponse to atezolizumab plus CYT107 can be correlated with specific microbiota.

Assays will be performed in collaboration with Dr. [redacted] at Fred Hutch or other agreed upon collaborator.

***Hypothesis**:* The gut microbiome profile will affect the clinical response to the combination of atezolizumab with CYT107 to a yet unknown extent.

2.7 Special Studies

2.7.1 *Assessment of Immunogenicity and Pharmacokinetics*

The known and predicted activities of these two immunotherapeutic agents in enhancing immune responses may, in combination, influence pharmacokinetics and immunogenicity. In particular CYT107 is pharmacologically targeting lymphocytes and subject to a PK target mediated clearance (like many other blood growth factors). This is the case for G-CSF and other factors. We have validated methods to measure CYT107 blood samples for PK analysis as well as to detect and measure the presence of binding and neutralizing antibodies. We will thus measure CYT107 blood levels before the first and fourth administrations of CYT107, and at specified intervals after administration of CYT107. This would enable detection of any potential significant interference of the concomitant immunotherapies on CYT107 PK. Similarly, we will measure anti-CYT107 binding antibodies before any CYT107 administration and after the last CYT107 administration. Any subject presenting with binding antibodies will be further tested for the presence of anti-CYT107 neutralizing antibodies. While the number of patients will be too small to draw definitive conclusions, this might lead to a potential interference in the combination therapy deserving a further exploration.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically documented locally advanced/inoperable or metastatic UBC, including renal pelvis, ureters, urinary bladder, and urethra.

***Note**:* Mixed histology tumors allowed if predominant histology is urothelial carcinoma.

***Note**:* Small cell or neuroendocrine carcinoma is not allowed if predominant.

3.1.2 Patients must have recurrent disease after any prior platinum-based chemotherapy regimen.

3.1.3 Patients must have measurable disease per RECIST 1.1 assessed by computed tomography (CT) scan or MRI. See Section 11 for the evaluation of measurable disease.

3.1.4 Patients must be ≥18 years of age on day of signing informed consent document.

Because no dosing or adverse event data are currently available on the use of atezolizumab in combination with CYT107 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

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

3.1.6 Patients must have a life expectancy of greater or equal to 12 weeks

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

– leukocytes	≥2,500/mcL
– absolute neutrophil count	≥1,000/mcL
– platelets	≥100,000/mcL
– hemoglobin	≥8 g/dL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN) (however, patients with known Gilbert's disease who have serum bilirubin level ≤3 × ULN may be enrolled)
– AST(SGOT)/ALT(SGPT)	≤3 × ULN (AST and/or ALT ≤5 × ULN for patients with liver involvement)
– alkaline phosphatase	≤2.5 × ULN (≤5 x ULN for patients with documented liver involvement or bone metastases)
– creatinine clearance	≥30 mL/min/1.73 m^2 by Cockcroft-Gault: $\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$

	At the discretion of the treating physician, a 24-hour urine creatinine clearance could be obtained and utilized as the gold standard if creatinine clearance by Cockcroft-Gault is <30, and prevents patient enrollment on the trial.
– 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.)

3.1.8 Patients must provide tissue from an archival tumor sample (obtained within 2 years from screening visit) or newly obtained core, punch, or excisional biopsy of a tumor lesion if deemed relatively safe and technically feasible.

3.1.9 Female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours before receiving the first dose of study agent(s). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Administration of atezolizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. CYT107 has not been tested for reproductive toxicity yet and may expose to the same risk. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) before study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of study agent. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.10 Patients must have the ability to understand and the willingness to sign a written informed consent document.

3.1.11 Patients positive for HIV are allowed on study, but HIV-positive patients must have:

a. A stable regimen of 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 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 2 weeks (4 weeks for nitrosoureas or systemic mitomycin C) before the initiation of study treatment.

3.2.3 Patients who have received more than 2 systemic cytotoxic chemotherapy regimens for metastatic urothelial carcinoma.

***Note**:* Prior perioperative chemotherapy is allowed and is not counted as a line of therapy if patient relapsed ≥12 months later and received additional platinum-based chemotherapy for metastatic disease.

3.2.4 Patients who have not recovered from adverse events (other than alopecia) due to agents administered more than 4 weeks earlier (*i.e.,* have residual toxicities >Grade 1). However, the following therapies are allowed:

- Hormone-replacement therapy or oral contraceptives
- Herbal therapy ≥1 week before initiation of study treatment (herbal therapy intended as anticancer therapy must be discontinued at least 1 week before initiation of study treatment)
- Palliative radiotherapy for bone metastases >2 weeks before initiation of study treatment

3.2.5 Patients who have received prior treatment with anti-PD-1, or anti-PD-L1 therapeutic antibody, or pathway-targeting agents.

- Patients who have received prior treatment with anti-CTLA-4 may be enrolled, provided the following requirements are met:
  - Minimum of 12 weeks from the first dose of anti-CTLA-4 and >6 weeks from the last dose
  - No history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)

3.2.6 Patients who have received treatment with any other investigational agent within 4 weeks before initiation of study treatment.

3.2.7 Patients who have received treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-α or interleukin [IL]-2) within 6 weeks before initiation of study treatment.

3.2.8 Patients who have received treatment with systemic immunosuppressive medications (including, but not limited to, oral prednisone (>10 mg/day or equivalent), cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor [anti-TNF] agents) within 2 weeks before initiation of study treatment.

- 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.

3.2.9 Patients taking bisphosphonate therapy for symptomatic hypercalcemia.

Note: Use of bisphosphonate therapy for other reasons (*e.g.,* bone metastasis or osteoporosis) is allowed.

3.2.10 Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases are excluded, with the following exceptions:

- Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
  - No neurosurgical resection or brain biopsy within 28 days before initiation of study treatment
- Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
  - Radiographic demonstration of improvement upon the completion of CNS directed therapy and no evidence of interim progression between the completion of CNS directed therapy and the screening radiographic study
  - No stereotactic radiation or whole-brain radiation within 28 days before initiation of study treatment
  - Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

Note: Patients with CNS metastases enrolled on trial must also have a brain MRI imaging at all standard radiologic evaluation timepoints (refer to Section 10)

3.2.11 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.12 Patients who have a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

3.2.13 Patients with known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver/NAFLD/NASH; 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) are eligible.

- Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

3.2.14 Patients with active underlying autoimmune disease requiring systemic immunosuppressive medication (oral prednisone >10 mg/day or equivalent). Topical, inhaled, or intraarticular steroids or physiologic endocrine replacement (insulin, levothyroxine, etc.) are permitted. Patients with a history of autoimmune disease that is not currently active require consultation with the Protocol PI and/or CITN Coordinating Center.

3.2.15 Patients who have a history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (bronchiolitis obliterans, cryptogenic organizing pneumonia, *etc.*), or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.2.16 Patients who have known additional malignancies other than UBC within 2 years before initiation of study treatment.

Exceptions include malignancies with a negligible risk of metastasis or death and treated with expected curative outcome (*e.g.,* non–melanomatous skin cancers), or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer.

3.2.17 Patients with active tuberculosis (TB).

3.2.18 Patients who have leptomeningeal disease.

3.2.19 Patients who have severe infections within 4 weeks before initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.

Exception: Uncomplicated urinary tract infection will not be considered as a severe infection in these patients.

3.2.20 Patients who have signs or symptoms of infection within 2 weeks before initiation of study treatment.

3.2.21 Patients who have received oral or IV antibiotics within 2 weeks before initiation of study treatment. Patients receiving prophylactic antibiotics (*e.g.,* for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

3.2.22 Patients who have major surgical procedure, other than for diagnosis, within 28 days before initiation of study treatment or anticipation of need for a major surgical procedure

during the course of the study.

3.2.23 Patients who have had a live, attenuated vaccine within 4 weeks before initiation of study treatment or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of atezolizumab.

- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks before initiation of study treatment or at any time during the study.

3.2.24 Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure (New York Heart Association Class III or IV), unstable angina pectoris, cardiac arrhythmia, recent myocardial infarction (within the last 6 months), or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.25 Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or medical (*e.g.,* infectious) illness.

3.3 Inclusion of Women and Minorities

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

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. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 CTSU Registration Procedures

This study is supported by the NCI CTSU.

4.2.1 *IRB Approval*

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should

continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a participating organization (PO); and
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 *Downloading Site Registration Documents*

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to the institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen;
- Either enter the protocol number in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select *CITN*, and protocol *CITN-14*.
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 *Submitting Regulatory Documents*

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

4.2.4 *Checking **Site** Registration Status*

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration*; and
- Enter your 5-character CTEP Institution Code and click on Go;
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

***Note**:* The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. 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 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task

assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.4 Patient Enrollment

4.4.1 *OPEN*

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available to users on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Before accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU member's website. Further instructional information is on the OPEN section 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.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.5 General Guidelines

After registration, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the PI. If a patient does not receive protocol therapy after registration, the patient's registration on the study may be canceled. The Clinical Research Site (CRS) must notify the CITN Coordinating Center of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP.

5. TREATMENT PLAN

This is a phase II trial of atezolizumab (MPDL3280A) plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma. The trial follows a randomized, controlled trial design, with an initial 'Safety Run-In' phase designed to evaluate the acute safety profile of the investigational treatment combination.

During the Safety Run-In phase, 6 patients will be assigned to the experimental arm (atezolizumab + CYT107) with staggered enrollment. This will be accomplished with an initial 3 patient enrollment. All adverse events will be assessed by the Toxicity Evaluation Committee. If 0-1 patient experiences a protocol-defined DLT (refer to Section 5.2) after completion of the 4-week DLT window, an additional 3 patients will be enrolled. Once all 6 patients have completed the 4-week DLT window, the Toxicity Evaluation Committee will again assess all adverse events. If, at any time, 2 or more patients experience a protocol-defined DLT, further enrollment into the trial will be suspended.

If the treatment combination of the experimental arm demonstrates an acceptable safety profile in the Safety Run-In (one or fewer patient experiences a protocol-defined DLT), randomized enrollment into the trial will begin.

Patients will be randomly assigned to either the control arm (atezolizumab monotherapy) or experimental arm (atezolizumab + CYT107) of the trial.

The first 6 subjects enrolled in the run-in phase of the study will have PK sampling done at baseline (prior to CYT107 administration), and at week 4 prior to CYT107 administration and at 2 hours, 4 hours and 6 hours after the fourth CYT107 administration.

Anti-drug antibody testing (ADA testing) will be done on all subjects who receive CYT107. Testing will be done at baseline (prior to CYT107 administration) and at week 8, (1 month after

the last CYT107 administration.) Any subject who develops binding antibodies will be further tested for the presence of anti-CYT107 neutralizing antibodies.

Randomization in the OPEN system may be performed up to 5 business days before initiation of study treatment to allow for clinical site logistics.

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.

Regimen Description					
EXPERIMENTAL ARM					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Atezolizumab	antihistamines or antipyretics/ analgesics[1]	1200 mg	IV	Day 8 of Cycle 1 (28-day cycle) and Day 1 of Cycle 2+ (21-day cycles)	Cycle 1: 28 days Cycle 2+: 21 days
IL-7 (CYT107)[2]	None	10 mcg/kg	IM	Days 1, 8, 15 and 22 of Cycle 1 ***only***	
CONTROL ARM					
Atezolizumab	antihistamines or antipyretics/ analgesics[1]	1200 mg	IV	Day 1 of each cycle	21 days

Note: [1]Premedication ***not*** permitted for the first dose on either arm; [2]Calculate the required dose amount (10 mcg/kg) based on patient's baseline weight. The dose amount should be recalculated if the patient's weight changes by more than 10% from the baseline weight measurement.

5.1.1 *Atezolizumab*

All patients enrolled into this study will receive atezolizumab. Atezolizumab will be administered on Day 1 of each 21-day cycle in the control arm. Atezolizumab will be administered on Day 8 of Cycle 1 (28-day cycle) and on Day 1 of each subsequent cycle (21-day cycle) on the experimental arm. Atezolizumab may be administered up to 2 days before or after the scheduled administration date of each cycle due to administrative reasons.

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.

Atezolizumab will be administered following the CYT107 injection on Day 8 of Cycle 1 for patients enrolled in the Safety Run-in Phase and experimental arm.

For anaphylaxis precautions, see the management guidelines below. Atezolizumab infusions will be administered per the instructions outlined in the Table below.

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion–related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion–related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, IV, intramuscular, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

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

- Stop the study drug infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.

- Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observation.

All patients randomly assigned to the experimental treatment arm in Part 2 will also receive CYT107 in addition to atezolizumab.

5.1.2 *Recombinant Human IL-7 (CYT107)*

Patients enrolled in the Safety Run-in phase and patients randomly assigned to the experimental arm of the trial will receive recombinant human IL-7 (CYT107). The patients will receive 10 mcg/kg of IL-7 (CYT107) IM on days 1, 8, 15 and 22 of Cycle 1 only. The CYT107 dose must be administered before atezolizumab on Day 8 of Cycle 1.

For patient with a Body Mass Index (BMI) >30, an adjusted body weight will be used to calculate the final dose the patient will receive. Please refer to Appendix D for details on the adjusted body weight calculation.

Patients receiving CYT107 will have their vital signs (heart rate, respiratory rate, blood pressure, and temperature) determined within 60 minutes before the first CYT107 injection on day 1, and 2 hours (±15 minutes) after the injection.

On day 8, vital signs will be monitored as described above (Section 5.1.1) following the guidelines for the first atezolizumab infusion.

On days 15 and 22, vital signs will be determined within 60 minutes before and within 30 minutes after the injection.

Patients will be informed about the possibility of the development of an allergic reaction to CYT107 (hives, bronchospasm, rash, *etc.*) and instructed to contact their study physician if they develop such symptoms.

5.1.3 *Other Procedures: Biopsy (core needle, punch or excisional)*

The rationale for the biopsy/tissue collection is to investigate changes in the tumor microenvironment that may correlate with response or provide information on potential actionable causes for lack of benefit.

A pre-treatment biopsy/tissue collection will be obtained before the first dose of study treatment (atezolizumab or CYT107) assuming this can be carried out safely.

Note: If an archival tumor sample (at least 0.5 × 0.5 × 0.5 cm) obtained within 2 years from screening visit is available, the pre-treatment biopsy is not required.

A post-treatment tumor biopsy/tissue collection will be obtained if deemed relatively safe and technically feasible (core biopsy, punch biopsy or excisional biopsy). The tumor biopsy/tissue collection will be obtained prior to dosing on Cycle 4, Day 1*or* at the end of treatment visit, whichever occurs first.

The biopsies will be done according to clinical site Standard Operating Procedures (SOPs).

5.1.4 *Other procedures: Microbiome Sample Collection*

Pre-treatment and post-treatment microbiome samples will be collected by patients using standard, at home stool-collection procedures using standardized fecal swab/storage devices. The samples will be stored frozen at home by patient and returned to the clinical research site at their next study visit.

Patients will be provided with fecal swab/storage devices and instructions (refer to Appendix E) at the screening visit and at the Cycle 3, Day 1 visit.

5.2 *Safety Run-in*: Definition of Dose-Limiting Toxicity

Dose-limiting toxicity is defined as any adverse event (AE) occurring within the first 28 days (*i.e.,* from Week 1 Day 1 through Week 4 Day 7), that is considered to be ***at least possibly related*** to the protocol treatment (atezolizumab, CYT107 or both), and that meets at least one of the non-hematologic or hematologic criteria below:

5.2.1 *Hematologic toxicity*

The standard NCI Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 criteria will be replaced by these criteria:

- Any Grade 4 event, including laboratory electrolyte abnormalities, that is not easily reversed without sequelae
- Grade 4 neutropenia (Absolute Neutrophil Count (ANC) <0.5 × 109/L)
- Grade 3 febrile neutropenia (ANC <1.0 × 109/L with a fever ≥38.3ºC)
- Grade 4 thrombocytopenia (<25.0 × 109/L) lasting >4 days or that requires platelet transfusion
- Grade ≥3 thrombocytopenia (<50.0–25.0 × 109/L) associated with Grade ≥3 bleeding
- Grade 2 concurrent AST or ALT >3xULN and total bilirubin > 2xULN without evidence of cholestasis
- Any toxicity resulting in death (*i.e.,* Grade 5)

Note*:* Peripheral lymphocytopenia after the first CYT107 injection is not a sign of toxicity; it reflects the lymphocytes "homing effect" of *rh*IL-7. Lymphocyte counts usually come back to baseline 5 to 7 days after the first injection.

5.2.2 *Non-hematologic toxicity*

Any Grade ≥3 non-hematologic toxicity (CTCAE v5.0), ***except*** for the following, which will not constitute DLTs:

- Grade ≥3 nausea or vomiting lasting ≤72 hours with the use of adequate/maximal medical intervention and/or prophylaxis

- Grade 3 diarrhea lasting ≤72 hours with the use of adequate/maximal medical intervention and/or prophylaxis
- Grade 3 fatigue lasting ≤7 days
- Grade 3 injection site reaction (unless operative intervention is required)
- Grade 3 hyperglycemia lasting ≤72 hours with standard antidiabetic therapy
- Grade 3 increases in liver transaminases (>5.0–20.0 × ULN) in patient with liver metastases
- Clinical laboratory abnormalities that are reversible to ≤Grade 1 or baseline status within 72 hours with outpatient care and/or monitoring, or that are considered not clinically significant by the treating physician

Management and dose modifications associated with the above AEs are outlined in Section 6.

The AEs will be assessed by the Toxicity Evaluation Committee, which includes the PI(s), study sponsor(s), CTEP and the CITN Central Operating and Statistical Center (COSC).

The patients must complete the full 4-week DLT window to be considered evaluable for DLTs. Patients who discontinue from the study before completion of the full 4-week DLT window for reasons other than the occurrence of a DLT (*e.g.,* withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

All randomly assigned patients will be monitored for occurrence of DLT. Monitoring of all safety and toxicity data is done by the PI, the study Sponsor(s) and the CITN COSC on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites must notify the PI and CITN COSC when a DLT has occurred.

A delay due to toxicity in receiving the second cycle of therapy of >14 days will be considered a DLT in subjects enrolled in the safety run-in phase of the study. This does not apply to subsequent subjects enrolled in the randomized component of the study.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Atezolizumab and CYT107 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently updated medical reference for a list of drugs to avoid or minimize use of.

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 baseline 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) should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

5.3.1 *Atezolizumab Excluded Therapies*

Any concomitant therapy intended for the treatment of cancer, whether health authority approved or experimental, is prohibited unless it is specifically included in the treatment regimen described in this protocol. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 5.3.1).
  - After Cycle 1, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (*e.g.,* treatment of known bony metastases); atezolizumab administration may be suspended during radiotherapy.
- Herbal therapy intended as anticancer therapy must be discontinued ≥1 week before initiation of study treatment; 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.

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.

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.

5.3.2 *Recombinant Human IL-7 (CYT107)*

The excluded therapies listed above (Section 5.3.1) also apply to CYT107. Immunostimulatory and immunosuppressive agents are prohibited.

Topical corticosteroids to treat injection site reaction are allowed.

Studies performed to investigate the potential of CYT107 to inhibit or to act as a time dependent inhibitor of hepatic microsomal cytochrome P450 isozymes (see Investigator Brochure) concluded that at the concentration investigated, it is unlikely that CYT107 will be involved in drug-drug interactions and CYT107 is not expected to cause clinically significant P450 inhibition or induction. However, the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies including vitamins and nutritional supplements.

5.4 Duration of Therapy

In the absence of treatment delays due to AE(s), treatment may continue for *up to 2 years* or until one of the following criteria applies:

- Disease progression warranting alternative systemic therapy,

***Note**:* Patients with radiographic progressive disease (PD) who are otherwise stable without symptomatic progression may continue Atezolizumab until the next radiographic imaging time point (within 9 weeks) to assess for possible pseudoprogression.

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable AE(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Patient noncompliance,
- Dosing interruption lasting >12 weeks (see Section 6.1.1),
- Pregnancy
  - All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.,* missed or late menstrual period) at any time during study participation.
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor(s), or
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the CRF.

All patients who tolerate the protocol regimen and with either complete tumor response (CR), partial response (PR), or stable disease (SD) will be permitted to continue treatment with atezolizumab until confirmed disease progression or for up to 2 years.

Discontinuation of treatment may be considered, at the discretion of the treating physician, for patients who have attained a confirmed CR that have been treated for at least 24 weeks with atezolizumab and had at least 2 treatments beyond the date when the initial CR was declared.

5.5 Study Treatment beyond Disease Progression

Immunotherapeutic agents such as atezolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Patients with radiographic PD who are otherwise stable without symptomatic progression may continue trial treatment as long as they meet the following criteria (following consultation with Protocol PI and/or CITN Coordinating Center):

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease or threat to vital organs
- Absence of progressive tumor at critical anatomical sites (*e.g.,* cord compression) requiring urgent alternative medical intervention

Patients should remain on the trial and continue to receive monitoring according to the Study Calendar (Section 10).

5.6 Duration of Follow-Up

The active study will end when the last patient reaches 2 years.

Disease status and overall survival data will be collected and reported every 12 weeks, either by in-person visit or by telephone assessment.

Upon discontinuation of study treatment in patients without documented progression, every effort should be made to continue monitoring disease status by radiologic imaging at the investigative site or locally. Imaging will be collected and evaluated per RECIST 1.1. Patients will be followed for disease assessment for *up to 2 years* after discontinuation of study treatment.

Standard of care disease assessments will be collected until disease progression, start of new anticancer treatment, death or end of study, whichever occurs first.

After disease progression or start of new anticancer treatment, patient will be followed for overall survival only. Survival follow-up will continue until death or the end of the study, whichever occurs first.

Patients removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE; in addition, the patients will be followed for disease status and overall survival, as described above.

5.7 Patient Replacement

All randomly assigned patients who receive at least one dose of the investigational treatment will be considered evaluable for safety and included in the overall safety analysis.

During the Safety Run-in Phase, patients who discontinue from the study before completion of the full 4-week DLT window for reasons other than the occurrence of a DLT (*e.g.,* withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

6. DOSING DELAYS/DOSE MODIFICATIONS

The NCI CTCAE Version 5.0 will be used to grade AEs. Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in this section.

Patients will be evaluated for AEs (all grades), serious AEs, and AEs requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

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.

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.

For detailed information regarding management of AEs 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 before 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 before, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

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 Section 5.1.1, including the '**Administration of First and Subsequent Atezolizumab Infusions**' table for guidelines for the management of Infusion-Related Reactions and Anaphylaxis.

Atezolizumab has been associated with risks such as the following: IRRs and immune–related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

6.1.2.1 *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 and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

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

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or appropriate delegate).

6.1.2.2 *Hepatic events*

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

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

have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

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

Event	Management
Guidelines for patients without hepatocellular carcinoma	
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of >5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Guidelines for patients with hepatocellular carcinoma	

Event	Management
AST/ALT is within normal limits at baseline and increases to >3×ULN to ≤10×ULN **or** AST/ALT is >ULN to ≤3×ULN at baseline and increases to >5×ULN to ≤10×ULN **or** AST/ALT is >3×ULN to ≤5×ULN at baseline and increases to >8×ULN to ≤10×ULN	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Monitor LFTs more frequently until return to baseline values. • For events of > 5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
AST or ALT increases to >10×ULN or total bilirubin increases to >3×ULN	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over ≥1 month.

Event	Management

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.3 *Gastrointestinal events*

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

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

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.4 *Endocrine disorders*

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

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) levels should be obtained to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (*e.g.*, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone

[ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence may be an indication of beta-cell destruction and atezolizumab-induced diabetes. If patient has Type 1 diabetes (*e.g.* new-onset diabetes in the absence of corticosteroids or another inciting medication), treat as a Grade 3 event. • Exercise caution in utilizing non-insulin hypoglycemic agents in this setting, as new-onset hyperglycemia in the absence of corticosteroids may be an indication of beta-cell destruction and atezolizumab-induced diabetes. After a thorough investigation of other potential causes which may involve a referral to an endocrinologist, follow institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Strongly consider referral to endocrinologist, particularly if patient is deemed to have atezolizumab-induced diabetes; if so, obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level. • If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, etc.) reported. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 12 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.5 *Ocular Events*

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

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

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.6 *Immune-mediated Myocarditis*

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (*e.g.*, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, *e.g.*, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

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

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

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.7 *Infusion-Related Reactions and Cytokine-Release Syndrome*

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, and/or analgesics (*e.g.*, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis. IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee *et al*., 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz *et al*., 2017; Adashek and Feldman, 2019), including atezolizumab.

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

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin, 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Event	Management
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the investigator.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.

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

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

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

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab

should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler *et al*. (2019).

6.1.2.8 *Pancreatic Events*

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

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.9 *Dermatologic Events*

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

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (*e.g.*, antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone

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

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.10 *Immune-mediated 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 the table below.

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.11 *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 below.

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.12 *Renal Events*

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

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

Event	**Management**
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.13 *Immune-Mediated Myositis*

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

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

Event	**Management**
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

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

Event	Management

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

6.1.2.14 *Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome*

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

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

- Fever ≥38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin <90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants <4 weeks old)
  - Platelet count $<100 \times 10^9$/L (100,000/mcL)
  - ANC $<1.0 \times 10^9$/L (1000/mcL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

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

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/mcL)
  - AST ≥48 U/L

- Triglycerides >1.761 mmol/L (156 mg/dL)
- Fibrinogen ≤3.6 g/L (360 mg/dL)

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

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

6.2 Recombinant Human IL-7 (CYT107)

There will be no dose reduction for CYT107 in this study.

Delays in dosing will be allowed for delays such as weather factors resulting in delays getting to the clinic or hospital, travel delays, clinic schedules, or emergencies. A delay of up to *72 hours* will be allowed on one occasion during the course of a treatment cycle.

Patients will come off protocol therapy if any CYT107 or treatment-related grade 3 or 4 AEs by CTCAE Version 5.0 criteria occur with the ***exception*** of transient lymphopenia. Three cases of Grade 3 lymphopenia have been documented with CYT107. Peripheral lymphopenia after the first CYT107 injection is a sign of CYT107 activity; reflecting the *rh*IL-7 'homing effect' of lymphocytes to deep tissues.

For purposes of this trial, since peripheral lymphopenia is a transient event, a Grade 3 'lymphocyte count decrease' to <500-200 cells/mm^3 and a Grade 4 'lymphocyte count decrease' to <200 cells/mm^3 will not require patients coming off protocol provided the lymphocyte count returns to a minimum of 500 cells/mm^3 by the time of the scheduled start of the next weekly dose within the treatment phase. A Grade 3 or 4 'lymphocyte count decrease' will require patients coming off protocol if the count fails to return to a minimum of 500 cells/mm^3 by the time of the scheduled start of the next weekly dose.

Dose modifications for Adverse Events: Substantial AEs are not expected and thus dose modifications are not planned or recommended. In all human trials with CYT107, AEs were frequent, but transient and grade 2 or less (as noted in the Adverse Event list, Section 7.1.2). These include injection site reactions, lymphadenopathy, pyrexia, rash, and fatigue.

Below are dose management tables for the following AEs: fatigue, nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, and hepatic damage.

Event Name	**Fatigue**
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Hold* until ≤Grade 2
Grade 4	Off protocol therapy
*Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Physician discretion	

Event Name	**Nausea**
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy if with adequate/maximal medical intervention symptoms persist
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Antiemetics	

Event Name	**Vomiting**
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy if with adequate/maximal medical intervention symptoms persist
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Antiemetics	

Event Name	**Diarrhea**
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy if with adequate/maximal medical intervention symptoms persist
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Physician discretion	

Event Name	Neutropenia
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Hold* until ≤Grade 2
Grade 4	Off protocol therapy
*Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Treatment of infection as appropriate	

Event Name	Thrombocytopenia
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Platelet transfusions if indicated	

Event Name	Hepatic Damage
Grade of Event	**Management/Next Dose of CYT107**
≤Grade 1	No change in dosing schedule
Grade 2	No change in dosing schedule[1]
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients requiring a delay of >72 hours should go off protocol therapy.	
Recommended management: Physician discretion	

Note: [1]CYT107 will be discontinued if patients have a concurrent elevation of ALT >3 × ULN and total bilirubin >2 × ULN in whom there is no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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 (Sections 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 (CAEPR)

The CAEPR list provides a single list of reported and/or potential AE associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a

subset of AEs, 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.

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 Atezolizumab (MPDL3280A, NSC 783608)*

Below is the CAEPR for Atezolizumab. Frequency is provided based on 3097 patients.

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**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]	
	Hyperthyroidism[2]		
		Hypophysitis[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)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[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 INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	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]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Myasthenia gravis[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		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]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Skin and subcutaneous tissue disorders - Other (exanthematous pustulosis)[2]	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

*Denotes AEs that are <3%.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all PIs 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 email.

[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 AEs probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. AEs potentially related to atezolizumab may be manifestations of immune-mediated AEs. 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 after administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

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:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
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; Respiratory failure
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 AE currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 *CAEPRs for Recombinant Glycosylated Human Interleukin-7 (CYT107, NSC 767713)*

Below is the CAEPR for CYT107. Frequency is provided based on 402 patients.

Version 2.0, February 27, 2018[1]

Adverse Events with Possible Relationship to Recombinant Glycosylated Human Interleukin-7 (CYT107) (CTCAE 5.0 Term) [n= 402]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			

Adverse Events with Possible Relationship to Recombinant Glycosylated Human Interleukin-7 (CYT107) (CTCAE 5.0 Term) [n= 402]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Blood and lymphatic system disorders - Other (lymphadenopathy)		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		
	Fever		
	Injection site reaction		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all PIs 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 email.

Adverse events reported on recombinant glycosylated human interleukin-7 (CYT107) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that recombinant glycosylated human interleukin-7 (CYT107) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia
GASTROINTESTINAL DISORDERS - Abdominal pain; Rectal hemorrhage
IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Lymphocyte count decreased; Platelet count decreased
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Purpura
VASCULAR DISORDERS - Phlebitis

Note: Recombinant Glycosylated Human Interleukin-7 (CYT107) 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.

7.1.3 *Adverse Event List(s) for Commercial Agent(s)*: N/A

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade**: The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting. 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 *Rave-CTEP-AERS Integration*

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 Days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*, and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

7.3.2 *Distribution of Adverse Event Reports*

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: PI 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 email 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 PD 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.

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 AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE 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 *Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions:* N/A

7.3.5 *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:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, hypophysitis, and adrenal insufficiency
- Hepatitis, including AST or ALT >10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, or infusion-related reactions
- Nephritis
- Ocular toxicities (*e.g.,* uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (*e.g.,* atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis, bullous, toxi epidermal necrolysis)

7.4 Routine Adverse Event Reporting

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

AE 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 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 150 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 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 after 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.

7.7 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 AEs 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: Tecentriq™, MPDL3280A

Classification: monoclonal antibody

M.W.: 150 KD

Mode of Action: anti-PD-L1

Description:
Atezolizumab is a humanized IgG1 monoclonal antibody consisting of 2 heavy chains (448 amino acids) and 2 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. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with 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 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused with or without a low-protein binding 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), or polyethylene (PE).The prepared solution may be stored at 2°C–8°C for up to 24 hours or at ambient ≤ 25°C (77°F) for 6 hours from the time of preparation. If the dose solution is stored at 2°C–8°C (36°C–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. These times include the storage and administration times for the infusion. Do not shake or freeze infusion bags containing the dose solution.

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 IV 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 IV 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 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 patients 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.

Atezolizumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.4).

8.1.2 *CYT107 (Recombinant Glycosylated Human Interleukin-7) (NSC 767713)*

Other Names: Human Interleukin-7, Lymphopoietin-1, rHuIL-7

Classification: Cytokine

M.W.: 22kDa

Mode of Action: Multifunctional cytokine critical for T-cell development and homeostasis.

Description:
Glycosylated 152 amino acid recombinant protein containing three N-glycosylation sites and one O-glycosylation site, with 3 disulfide bridges: Cys2- Cys 92, Cys 34- Cys 129, and Cys 47- Cys 141. CYT107 is produced using a Chinese Hamster Ovary cell line.

How Supplied: CYT107 is supplied by RevImmune and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI. Each single-use 0.6 mL vial contains 1200 mcg of CYT107 at a concentration of 2000 mcg/mL, as a sterile, clear, colorless solution containing 10mM Sodium Acetate, 100mM Sodium chloride, 50mM Glutamic acid, 50mM Arginine, pH approximately 5.

CYT107 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.4).

Preparation: Do not shake vials. Remove number of vials required for dose preparation from the freezer and thaw at refrigerated temperature (2-8°C) for 1 hour prior to dose preparation. Once thawed, inspect vials for any visible particulate matter. If observed, discard vials. Aseptically withdraw the required dose volume into a syringe for administration.

Storage: Store vials in their original box frozen at -20°C.

If a storage temperature excursion is identified, promptly return CYT107 vials to -20°C freezer 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 of the intact vials are ongoing. Do not re-freeze thawed vials. Intact vials may be removed from the freezer and kept at refrigerated temperature for a maximum of 12 hours prior to dose administration. Once dose is withdrawn into a syringe, administer immediately. If necessary, prepared syringes may be stored refrigerated for up to 6 hours prior to administration. Vials are for single-use only. Destroy any remaining contents following dose preparation.

Route and Method of Administration: Intramuscular (IM) injection. Inject slowly (over 10-20 seconds) into Deltoid muscle or muscle of the thighs or buttocks, away from joints, nerves or bones. Rotate injection sites with each injection.

Potential Drug Interactions: *In-vitro*, CYT107 did not inhibit isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. *In vitro*, CYT107 did not induce isoenzymes CYP1A, CYP2B6 and CYP3A4. At concentrations tested, it is unlikely CYT107 will cause drug-drug interactions.

Patient Care Implications: Advise study participants to use effective contraception while receiving study treatment and for at least 2 months after the last dose.

For patient with a Body Mass Index (BMI) >30, an adjusted body weight will be used to calculate the final dose to be administered. Please refer to Appendix D for details on the adjusted body weight calculation.

8.1.3 *Agent Ordering and Agent Accountability*

NCI-supplied agents may be requested by the PI (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.

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 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.

8.1.3.1 *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.

8.1.4 *Investigator Brochure Availability*

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP-IAM account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.5 *Useful Links and Contacts*

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@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://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.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

Specimens will be collected for several planned correlative studies. Many samples will be processed and stored to be run in batches. The CITN Immune Monitoring Laboratory will provide lab kits and shipping supplies. Specific instructions on numbers and types of tubes required for each visit are provided in the CITN-14 Laboratory Manual.

When blood volume or specimen material is limited, the correlative studies will be considered secondary to tests needed to make clinical decisions. Prioritization of secondary tests will be made based on technical considerations, total amount of sample from each individual subject, total number of samples acquired, total number of each assay performed, and information gained from the assays performed to date. The anticipated priority correlatives are:

Plasma/serum-based studies

1. Multiplex Cytokines – Multiplex ELISA
2. Kynurenine and tryptophan (Kyn/Trp) ratios and

Cell associated studies

1. Evaluation of peripheral CD4+ and CD8+ T-cell counts
2. T-Cell Receptor Repertoire Analysis – TCR sequencing
3. Evaluation of the effect of atezolizumab with and without CYT107 on circulating Lymphocyte and Monocyte numbers and Phenotype
4. Tumor-Associated Neoantigen discovery – Whole Exome Sequencing and RNAseq and Antigen Prediction
5. Antitumor Immune T-cell Responses

Biopsy associated studies

1. Slide-Based Immune Phenotype Panel – Multispectral IHC
2. Assessment of tumor biopsy by gene expression analysis -- Interferon γ (INFγ) Gene Expression Signature - NanoString® nCounter® Human Immunology V2 Panel and the nCounter® PanCancer Immune Profiling Panel

3. Assessment of PD-L1 expression at Baseline and Post-treatment – Immunohistochemistry (IHC)
4. Tumor-Associated Neoantigen discovery – Whole Exome Sequencing and RNAseq and Antigen Prediction

9.1 Integrated Correlative Studies

9.1.1 *Evaluation of peripheral CD4+ and CD8+ T-cell counts – Integrated Laboratory Correlative Study #1*

9.1.1.1 *Collection of Specimen(s)*

Blood draws will be performed by venipuncture on study subjects in Red-Top or Gold SST or other blood draw tubes as specified per local site SOP.

9.1.1.2 *Handling of Specimens(s)*

Blood Samples will be collected at room temperature and shipped ambient to the local clinical lab.

9.1.1.3 *Shipping of Specimen(s)*

Blood collection tubes will be shipped at ambient temperature to the designated local clinical, CLIA compliant laboratory the same day as the blood draw.

9.1.1.4 *Site(s) Performing Correlative Study*

Assays will be performed at each local clinical site. Assays are to be performed at each site by a CLIA compliant laboratory. The specific technique is not specified in the protocol.

9.1.2 *Slide-Based Immune Phenotype Panel – Multispectral IHC – Integrated Laboratory Correlative Study #2*

9.1.2.1 *Collection of Specimen(s)*

Formalin-fixed, paraffin-embedded archival tissue block(s) from tumor obtained within 2 years from the screening visit will be identified by the clinical site at the relevant pathology laboratories where they were processed and stored. Tissue blocks are preferred, however FFPE slides can substitute if blocks are unavailable. Alternatively, patients will undergo a pre-treatment biopsy (core, punch, or excisional) as part of this protocol. Patient will undergo a post-treatment biopsy (core, punch, or excisional) if deemed relatively safe and technically feasible as part of this protocol.

9.1.2.2 *Handling of Specimens(s)*

Formalin-fixed, paraffin-embedded archival tumor blocks will be requested by fax and phone by the clinical site from the relevant pathology laboratory by providing the patient's name, consent form, and date of collection. If patients undergo biopsy as part of this protocol, tissue will be placed in formalin for overnight shipping to the CIML.

9.1.2.3 *Shipping of Specimen(s)*

For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks or FFPE slide to be shipped at ambient temperature to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. After sectioning at the CIML, the CIML will coordinate shipment of unstained slides to Dr. [redacted] at Fred Hutch.

9.1.2.4 *Site(s) Performing Correlative Study*

Assays will be performed by Dr. [redacted] at Fred Hutch.

9.1.3 *Assessment of tumor biopsy by gene expression analysis -- Interferon γ (INFγ) Gene Expression Signature - NanoString® nCounter® Human Immunology V2 Panel and the nCounter® PanCancer Immune Profiling Panel – Integrated Laboratory Correlative Study #3*

9.1.3.1 *Collection of Specimen(s)*

Formalin-fixed, paraffin-embedded archival tissue block(s) from tumor obtained within 2 years from the screening visit will be identified by the clinical site at the relevant pathology laboratories where they were processed and stored. Alternatively, patients will undergo a pre-treatment biopsy (core, punch, or excisional) as part of this protocol. Patients will undergo a post-treatment biopsy (core, punch, or excisional) if deemed relatively safe and technically feasible as part of this protocol.

9.1.3.2 *Handling of Specimens(s)*

Formalin-fixed, paraffin-embedded archival tumor blocks will be requested by fax and phone by the clinical site from the relevant pathology laboratory by providing the patient's name, consent form, and date of collection. If patients undergo biopsy as part of this protocol, tissue will be placed in formalin for overnight shipping to the CIML.

9.1.3.3 *Shipping of Specimen(s)*

For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks (preferred) or FFPE slides (if blocks are unavailable) to be shipped at ambient temperature to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. After sectioning at the CIML, the CIML will coordinate shipment of unstained slides (or RNA) to NanoString®. Depending on the specific contract, RNA will be extracted from FFPE slides, either at NanoString® or the CIML, using established protocols (MAN-10050-02 Preparing Nucleic Acid from FFPE Samples for Use with nCounter® Assays).

9.1.3.4 *Site(s) Performing Correlative Study*
Assays will be performed by NanoString® Technologies in Seattle, WA, and analyzed using qualified analytic tools at the immunopathology lab of Fred Hutch.

9.1.4 *T-Cell Receptor Repertoire Analysis – TCR sequencing – Integrated Laboratory Correlative Study #4*

9.1.4.1 *Collection of Specimen(s)*
Specimens will include archived and prospectively obtained tumor biopsies and blood samples. Blood draws will be performed by venipuncture.

9.1.4.2 *Handling of Specimens(s)*
Biopsy samples will be placed in formalin and shipped to the CIML. Blood collection tubes will be shipped on day of blood draw for overnight delivery to the CIML.

9.1.4.3 *Shipping of Specimen(s)*
Whole blood and biopsies in formalin will be shipped ambient to the CIML. Blood will be processed to PBMC as described above. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate shipment of samples to Adaptive Biosciences.

9.1.4.4 *Site(s) Performing Correlative Study*
Samples will be analyzed at Adaptive Bioscience in Seattle, WA, or other agreed upon vendor or collaborator.

9.1.5 *Tumor-Associated Neoantigen discovery – Whole Exome Sequencing and RNAseq and Antigen Prediction – Integrated Laboratory Correlative Study #5*

9.1.5.1 *Collection of Specimen(s)*
Specimens will include archived tumor blocks (or FFPE slides) and prospectively obtained tumor biopsies and blood samples. Blood draws will be performed by venipuncture.

9.1.5.2 *Handling of Specimens(s)*
For archival samples, clinical sites will arrange for the formalin-fixed, paraffin embedded tumor specimens to be shipped at ambient temperature to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML where they will be embedded in paraffin. Paraffin blocks (or FFPE slides) will be stored at 4°C under desiccant.

Blood collection tubes will be shipped on day of blood draw for overnight delivery to the CIML. Blood will be processed to PBMC as described above and stored in liquid nitrogen. Nucleic acid will be extracted from PBMC and from biopsy specimens using vendor-specific protocols.

9.1.5.3 *Shipping of Specimen(s)*
Whole blood, archival tumor blocks (or FFPE slides) and biopsies in formalin will be shipped ambient to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate shipment of samples to the Fred Hutch immunopathology lab and/or agreed upon vendor.

9.1.5.4 *Site(s) Performing Correlative Study*
These analyses will be performed using qualified analytes and analytic tools at the immunopathology lab and shared resources of the Fred Hutch or at a vendor to be determined.

9.1.6 *Antitumor Immune T-cell Responses -- ELISPOT – Integrated Laboratory Correlative Study #6*

9.1.6.1 *Collection of Specimen(s)*
Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

9.1.6.2 *Handling of Specimens(s)*
Blood collection tubes (for subsequent PBMC isolation) will be shipped on day of blood draw for overnight delivery to the CIML.

9.1.6.3 *Shipping of Specimen(s)*
Blood collection tubes will be shipped overnight at ambient temperature to the CIML using CIML established SOPs. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate shipment via cryoport of cryopreserved PBMC in the event that a vendor or collaborator performs these studies.

9.1.6.4 *Site(s) Performing Correlative Study*
Assays will be performed in the CIML at Fred Hutch under the direction of Dr. [redacted] or an agreed upon vendor or collaborator.

9.2 Exploratory Correlative Studies

9.2.1 *Assessment of PD-L1 expression at Baseline and Post-treatment -- Immunohistochemistry (IHC) – Exploratory Laboratory Correlative Study #1*

9.2.1.1 *Collection of Specimen(s)*
Formalin-fixed, paraffin-embedded archival tissue block(s) from tumor obtained within 2 years from the screening visit will be identified by the clinical site at the relevant pathology laboratories where they were processed and stored. Tissue blocks are preferred, however FFPE slides can substitute if blocks are unavailable. Alternatively, patients will undergo a pre-treatment biopsy (core, punch, or excisional) as part of this protocol. Patients will undergo a post-treatment biopsy

(core, punch, or excisional) if deemed relatively safe and technically feasible as part of this protocol.

9.2.1.2 *Handling of Specimens(s)*
Formalin-fixed, paraffin-embedded archival tumor blocks will be requested by fax and phone by the clinical site from the relevant pathology laboratory by providing the patient's name, consent form, and date of collection. If patients undergo biopsy as part of this protocol, tissue will be placed in formalin for overnight shipping to the CIML.

9.2.1.3 *Shipping of Specimen(s)*
For archival samples, clinical sites will arrange for the formalin-fixed, paraffin-embedded tumor blocks (preferred) or FFPE slides (if blocks are unavailable) to be shipped at ambient temperature to the CIML. For biopsies done as part of this protocol, tissue in formalin will be shipped overnight at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. After sectioning at the CIML, the CIML will coordinate shipment of unstained slides to HistoGeneX (Naperville, IL)or other agreed upon vendor.

9.2.1.4 *Site(s) Performing Correlative Study*
Assays will be performed by HistoGeneX or other agreed upon vendor. Samples would be run in batches.

9.2.2 *Evaluation of the effect of atezolizumab with and without CYT107 on circulating Lymphocyte and Monocyte numbers and Phenotype – Exploratory Laboratory Correlative Study #2*

9.2.2.1 *Collection of Specimen(s)*
Blood draws will be performed by venipuncture on study subjects just before, during, and at end of treatment.

9.2.2.2 *Handling of Specimens(s)*
Blood Samples will be collected at room temperature and shipped ambient to the CIML the same day as the blood draw. The sample must be received at the CIML within 24 hours of blood draw.

9.2.2.3 *Shipping of Specimen(s)*
Blood collection tubes will be shipped at ambient temperature to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML.

9.2.2.4 *Site(s) Performing Correlative Study*
Quantification of PBMC and T-cell subsets will be performed under the direction of Dr. [redacted] in the CIML at Fred Hutch.

9.2.3 *Multiplex Cytokines -- Multiplex ELISA – Exploratory Laboratory Correlative Study #3*

9.2.3.1 *Collection of Specimen(s)*
Whole blood will be collected into red-top tubes by venipuncture.

9.2.3.2 *Handling of Specimens(s)*
Blood samples will be processed to frozen serum at the local labs and stored frozen at -80°C.

9.2.3.3 *Shipping of Specimen(s)*
Frozen serum vials will be shipped from clinical sites to the CIML. Clinical sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate shipments of serum to the Fred Hutch Shared Resource facility or other collaborator, as needed.

9.2.3.4 *Site(s) Performing Correlative Study*
Assays will be performed at the Fred Hutch Shared Resource facility or other agreed upon collaborator or vendor.

9.2.4 *Kynurenine and tryptophan (Kyn/Trp) Ratios and Plasma Arginine levels – Exploratory Laboratory Correlative Study #4*

9.2.4.1 *Collection of Specimen(s)*
Blood draws will be performed by venipuncture on study subjects at time points before, during, and after treatment.

9.2.4.2 *Handling of Specimens(s)*
Plasma will be isolated by the local laboratory and frozen at -80°C.

9.2.4.3 *Shipping of Specimen(s)*
Plasma samples will be batch shipped overnight on dry ice to the CIML. Sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate the shipment of samples to the agreed upon collaborator or vendor.

9.2.4.4 *Site(s) Performing Correlative Study*
Kynurenine and tryptophan and Arginine levels will be assessed at an agreed upon collaborator or vendor to be determined.

9.2.5 *Microbiome Analyses – Exploratory Laboratory Correlative Study #5*

9.2.5.1 *Collection of Specimen(s)*

Fecal samples will be collected by patients pre-treatment and post-treatment using standard, at home stool-collection procedures using standardized fecal swab/storage devices.

9.2.5.2 *Handling of Specimens(s)*

Samples will be initially stored frozen at home by patients and returned to the clinical research site at their next study visit and stored at the local site at -80°C.

9.2.5.3 *Shipping of Specimen(s)*

Frozen samples will be batch shipped overnight on dry ice to the CIML. Sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate the shipment of samples to Dr. [redacted] at Fred Hutch.

9.2.5.4 *Site(s) Performing Correlative Study*

Assays will be performed in collaboration with Dr. [redacted] at Fred Hutch or other collaborator.

9.3 Special Studies

9.3.1 *Immunogenicity Testing*

The formation of anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) to glyco-rhIL-7 (CYT107) will be evaluated in the Safety Run-In/Experimental Arm subjects only, on Cycle 1, Day 1 before the first CYT107 injection and on Cycle 3, Day 1. If positive on Cycle 3, Day 1, immunogenicity testing will be repeated at the end of the study.

9.3.1.1 *Collection of specimen(s)*

Blood draws will be performed by venipuncture on study subjects before, during and at end of treatment.

9.3.1.2 *Handling of specimen(s)*
Plasma will be isolated by the local laboratory and frozen at -80C.

9.3.1.3 *Shipping of Specimen(s)*
Plasma samples will be batch shipped overnight on dry ice to the CIML (Seattle, WA). Sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate the shipment of samples to the agreed upon collaborator or vendor.

9.3.1.4 *Site(s) Performing Immunogenicity Testing*
ADA and NADA to glyco-rhIL-7 (CYT107) will be performed by Eurofins Scientific (Vergeze, France) who will perform both ELISA Binding (non-neutralizing) and neutralizing antibody assays according to their Standard Operating Procedure.

9.3.2 *CYT107 Pharmacokinetics*

The pharmacokinetic profile of CYT107 levels will be assessed to determine if Atezolizumab has an effect on CYT107 PK levels. The samples will be collected before CYT107 treatment on Cycle 1, Day 1 and again on Cycle 1, Day 22.

9.3.2.1 *Collection of specimen(s)*
Blood draws will be performed by venipuncture on study subjects before and during study treatment.

Table 9.3.2 Pharmacokinetics timepoints

Cohort	Pharmacokinetic timepoints for CYT107
Safety Run-in subjects	Day 1, Immediate Pre-dose CYT107
Safety Run-in subjects	Day 1, 2 hours (± 15 mins) after CYT107 administration is complete
Safety Run-in subjects	Day 1, 4 hours (± 15 mins) after CYT107 administration is complete
Safety Run-in subjects	Day 1, 6 hours (± 15 mins) after CYT107 administration is complete
Safety Run-in subjects	Day 22, Immediate Pre-dose CYT107 and Atezolizumab
Safety Run-in subjects	Day 22, 2 hours (± 15 mins) after CYT107 administration is complete*
Safety Run-in subjects	Day 22, 4 hours (± 15 mins) after CYT107 administration is complete*
Safety Run-in subjects	Day 22, 6 hours (± 15 mins) after CYT107 administration is complete*
**Blood draws are timed after CYT107 administration is complete, not completion of Atezolizumab infusion.*	

9.3.2.2 *Handling of Specimens(s)*
Plasma will be isolated by the local laboratory and frozen at -80°C.

9.3.2.3 *Shipping of Specimen(s)*

Plasma samples will be batch shipped overnight on dry ice to the CIML (Seattle, WA). Sites will utilize a web-based specimen system (BSI-Web) to communicate with the CIML. The CIML will coordinate the shipment of samples to the agreed upon collaborator or vendor.

9.3.2.4 *Site(s) Performing Pharmacokinetics Testing*

PK of glyco-rhIL-7 (CYT107) will be performed by Eurofins Scientific (Vergeze, France) who will perform assays according to their Standard Operating Procedures.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days before the initiation of study treatment. Scans and x-rays must be done <4 weeks (28 days) before the initiation of study treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours before the initiation of the next cycle of therapy. Patients receiving atezolizumab will be assessed for pulmonary signs and symptoms throughout the study.

SAFETY RUN-IN/EXPERIMENTAL ARM																		
Treatment Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3**			**Subsequent Cycle (Repeat up to 2 year)**			**End of Tx**	**Post-Treatment Follow-up**		
Weeks	Screening visit	Wk1[a]	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	Wk13	At time of D/C ± 5 days	Safety FU	Disease Assessment[i]	Survival FU
Scheduling Window	Within 14 days	Day 1	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2		30 days ± 5 post DC	Every 12 ±1 weeks	Every 12 ±1 weeks
Atezolizumab			A			A			A			A						
CYT107		B	B	B	B													
Administrative procedures																		
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Concurrent meds	X	X----------X													X	X	X	X
Clinical Procedures/Assessments																		
Physical exam	X	X				X			X			X			X	X		
Vital signs[b]	X	X	X	X	X	X			X			X			X	X		
Height	X																	
Weight	X	X	X	X	X	X			X			X			X	X		
Adverse event evaluation		X----------X													X	X	X	
Immune-related AEs evaluation		X----------X													X	X	X	
Performance status	X	X	X	X	X	X			X			X			X	X		
EKG (as indicated)	X																	
Laboratory Assessments (Safety Labs)																		
CBC w/diff, plts	X	X	X	X	X	X			X			X			X	X		
Serum chemistry[c]	X	X	X	X	X	X			X			X			X	X		
Pregnancy Test (Urine or Serum HCG)	X[d]														X			
Efficacy Measurements																		
Tumor measurements	Within 28 days	Tumor measurements are repeated every *9±1 weeks*. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X		X	
Radiologic evaluation[k]	Within 28 days	Radiologic measurements should be performed every *9 ± 1 weeks.*													X		X	

SAFETY RUN-IN/EXPERIMENTAL ARM																		
Treatment Cycle		**Cycle 1**				**Cycle 2**			**Cycle 3**			**Subsequent Cycle** (Repeat up to 2 year)			**End of Tx**	**Post-Treatment Follow-up**		
Weeks	Screening visit	Wk1[a]	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	Wk13	At time of D/C ± 5 days	Safety FU	Disease Assessment[i]	Survival FU
Scheduling Window	Within 14 days	Day 1	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2		30 days ± 5 post DC	Every 12 ±1 weeks	Every 12 ±1 weeks
Tumor Biopsies/Archival Tissue Collection																		
Tumor Biopsy	X[e]											X[j]			X[j]			
Correlative Studies Blood Draws[h]																		
T cell (CD4+ and CD8+) count		X	X[f]	X	X	X[f]			X[f]			X[f]						
Immunophenotyping		X	X			X			X						X			
Multiplex Cytokines		X				X			X						X			
TCR sequencing		X	X			X			X									
ELISPOT		X				X			X									
Kyn/Trp and Arginine		X				X			X						X			
Microbiome	X[g]								X[g]									
PK CYT107[l]		X[l]			X[l]													
Immunogenicity CYT107		X[m]							X[m]						X[m]			

A: Atezolizumab: Dose as assigned; once every 3 weeks, starting Cycle 1, Day 8
B: *CYT107*: Dose as assigned; Cycle 1, Days 1, 8, 15 and 22; must be administered before atezolizumab on Cycle 1, Day 8
a: For patients receiving CYT107 (Run-In phase or Experimental arm) ***only***
b: Vital signs assessment before and after CYT107 injection and/or Atezolizumab infusion is required (section 5.1.1 and 5.1.2)
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, INR, aPTT.
d: Pregnancy test (women of childbearing potential) must be performed within 72 hours prior to initiation of study treatment.
e: Tumor biopsy tissue (archival or fresh) is required per eligibility criteria 3.1.8.
f: To be performed prior to the **first 4 doses and the 6th dose of atezolizumab**
g: Fecal swab/storage devices and instructions must be given to patient; sample collection to be performed at home by patient and returned to clinical research site at the next study visit (Cycle 1, Day 1 and Cycle 4, Day 1).
h: Correlative Studies Blood draws must be performed prior to study agent(s) administration on a dosing day.
i: Disease assessment per standard of care
j: Post-treatment tumor biopsy will be obtained prior to dosing on Cycle 4, Day 1 *or* at the End of Treatment visit, whichever occurs first.
k: Patients with known CNS metastases must also have a brain MRI imaging at all standard radiologic evaluation timepoints
l. PK (Pharmacokinetics) for CYT107 samples to be drawn on the first 6 patients enrolled in the run-in phase of the study, before the first and fourth administration and at 2hrs, 4 hrs, and 6 hrs after the first and fourth CYT107 administrations
m. Immunogenicity testing (anti-drug antibody testing or ADA testing) will be done on all subjects who receive CYT107. Testing will be done on Cycle 1, Day 1and on Cycle 3, Day 1. If positive on Cycle 3, Day 1, testing to be repeated at End of Treatment visit.

Baseline evaluations are to be conducted within 14 days before the initiation of study treatment. Scans and x-rays must be done <4 weeks (28 days) before the initiation of study treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours before the initiation of the next cycle of therapy. Patients receiving atezolizumab will be assessed for pulmonary signs and symptoms throughout the study.

CONTROL ARM

Treatment Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3**			**Subsequent Cycle** (Repeat up to 2 year)			**End of Tx**	**Post-Treatment Follow-up**		
	Screening visit	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	At time of D/C ± 5 days	Safety FU	Disease Assessment[h]	Survival FU
Scheduling Window	Within 14 days	Day 1	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2		30 days ± 5 post DC	Every 12 ±1 weeks	Every 12 ±1 weeks
Atezolizumab		A			A			A			A						
Administrative procedures																	
Informed consent	X																
Demographics	X																
Medical history	X																
Concurrent meds	X	X----------											----------X	X	X	X	X
Clinical Procedures/Assessments																	
Physical exam	X				X			X			X			X	X		
Vital signs[a]	X	X	X	X	X			X			X			X	X		
Height	X																
Weight	X	X	X	X	X			X			X			X	X		
Adverse event evaluation		X----------											----------X	X	X	X	
Immune-related AEs evaluation		X----------											----------X	X	X	X	
Performance status	X	X	X	X	X			X			X			X	X		
EKG (as indicated)	X																
Laboratory Assessments (Safety Labs)																	
CBC w/diff, plts	X	X	X	X	X			X			X			X	X		
Serum chemistry[b]	X	X	X	X	X			X			X			X	X		
Pregnancy Test (Urine or Serum HCG)	X[c]													X			
Efficacy Measurements																	
Tumor measurements	Within 28 days	Tumor measurements are repeated every *9±1 weeks*. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X		X	
Radiologic evaluation[j]	Within 28 days	Radiologic measurements should be performed every *9 ± 1 weeks.*												X		X	
Tumor Biopsies/Archival Tissue Collection																	
Tumor Biopsy	X[d]										X[i]			X[i]			

CONTROL ARM																	
Treatment Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3**			**Subsequent Cycle** (Repeat up to 2 year)			**End of Tx**	**Post-Treatment Follow-up**		
	Screening visit	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	At time of D/C ± 5 days	Safety FU	Disease Assessment[h]	Survival FU
Scheduling Window	Within 14 days	Day 1	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2		30 days ± 5 post DC	Every 12 ±1 weeks	Every 12 ±1 weeks
Correlative Studies Blood Draws[g]																	
T cell (CD4+ and CD8+) count		X[e]			X[e]			X[e]			X[e]						
Immunophenotyping		X			X			X						X			
Multiplex Cytokines		X			X			X						X			
TCR sequencing		X			X			X									
ELISPOT		X			X			X									
Kyn/Trp and Arginine		X			X			X						X			
Microbiome	X[f]							X[f]									

A: Atezolizumab: Dose as assigned; once every 3 weeks, starting Cycle 1, Day 1
a: Vital signs assessment before and after Atezolizumab infusion is required (section 5.1.1)
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, INR, aPTT.
c: Pregnancy test (women of childbearing potential) must be performed within 72 hours prior to initiation of study treatment.
d: Tumor biopsy tissue (archival or fresh) is required per eligibility criteria.
e: To be performed prior to the first 4 doses **and the 6th dose of atezolizumab**
f: Fecal swab/storage devices and instructions must be given to patient; sample collection to be performed at home by patient and returned to clinical research site at the next study visit (Cycle 1, Day 1 and Cycle 4, Day1).
g: Correlative Studies Blood draws must be performed prior to study agent(s) administration on a dosing day.
h: Disease assessment per standard of care
i: Post-treatment tumor biopsy will be obtained prior to dosing on Cycle 4, Day 1*or* at the End of Treatment visit, whichever occurs first.
j: Patients with known CNS metastases must also have a brain MRI imaging at all standard radiologic evaluation timepoints

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.

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 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.

This study will also evaluate response and progression using immune-related response criteria (irRC) [Wolchok 2009]. See Appendix C for a detailed description of the evaluation criteria.

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 CYT107.

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

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 noncystic 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 nonnodal 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. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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 after CR or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer)[Rustin 2004] and PSA response (in recurrent prostate cancer) [Bubley 1999; Scher 2008] have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [Vergote 2000].

Cytology, Histology These techniques can be used to differentiate between PR and 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 PD.

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 PI).

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.
*** 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: SD 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.

11.1.7 *Response Review*

Radiological images will be collected for a possible review of response by an expert(s) independent of the study. Measurement of tumor response by a trained radiologist/nuclear medicine physician at each clinical site will be chronicled and reported unless or until a central expert review takes place.

11.2 Other Response Parameters: Immune-Related Response Criteria (irRC)

See Appendix C for a detailed description of the evaluation criteria.

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 elsewhere in this section. The Protocol PI 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 AEs; reporting of expedited AEs; and accumulation of reported AEs from other trials testing the same drug(s). The Protocol PI and statistician have access to the data at all times.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via the mechanism described elsewhere in this section. All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Submission/Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site users must either click on the link in the email or log in to iMedidata via the CTSU members' website under Data Management > Rave Home and click to accept the invitation in the Tasks pane located in the upper right corner of the iMedidata screen. Site staff 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff 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 at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

12.2.1 *Method*

This study will be monitored by the CTMS. Data will be submitted to CTMS at least once every 2 weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11.

For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 *Responsibility for Data Submission*

For trials monitored by CTMS, a quarterly report of data will be provided by Theradex to the Coordinating Center.

12.3 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the PI and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

12.4 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 before 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 PI for non–Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment before 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 before submission, but in any case, before presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP before 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.

12.5 Genomic Data Sharing Plan: N/A

13. STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and methods for the study. If, after the study has begun, but before the conduct of any analysis, changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

13.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of Fred Hutch as part of the CITN.

13.2 Study Design/Objectives

This is a phase II trial of atezolizumab (MPDL3280A) plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma. The trial follows a randomized, controlled trial design, with an initial 'Safety Run-In' phase designed to evaluate the acute safety profile of the investigational treatment combination. The Safety Run-In phase is designed to demonstrate that the incidence of DLTs is 16.7% or less in 6 patients receiving the investigational combination. These patients will not be included as part of the overall analysis since they are not randomized. Due to the non-randomized nature of the enrollment for these six patients, the inclusion of these patients in the overall analysis could confound and bias results of any randomized comparisons. Hence, these 6 patients will be analyzed and reported separately both for safety and for efficacy. However, toxicity data from all patients will be reviewed in the aggregate at the time of the interim and final analysis to evaluate overall patterns.

The randomized trial is designed to evaluate the improvement in the objective response rate (ORR) of CYT107 + atezolizumab compared to atezolizumab alone in patients with advanced/unresectable bladder cancer who have progressive disease after a platinum-based chemotherapy regimen. An interim futility analysis will be conducted when 50% of planned sample size have their first disease assessment and survival information. An exploratory analysis will be conducted to evaluate the ORR after all patients have been followed up for 2 years.

13.2.1 *Primary Objective*

The primary endpoint will be the ORR, defined by CR or PR as measured by RECIST v1.1.

For patients with disease that progressed after at least one platinum-based treatment regimen, the ORR for atezolizumab monotherapy is 14.8%.

The Cochran Mantel Haenszel test will be conducted to compare ORR in the experimental arm (atezolizumab + CYT107) to the ORR in the control arm (atezolizumab monotherapy). A one-sided significance level of 0.10 will be considered for the test.

13.3 Sample Size/Accrual Rate

During the Safety Run-In phase, 6 patients will be assigned to the experimental arm (atezolizumab + CYT107) with staggered enrollment (refer to Section 5 for details). The AEs will be assessed by the Toxicity Evaluation Committee. If, at any time, 2 or more patients experience a protocol-defined DLT (refer to Section 5.2), further enrollment into the trial will be suspended.

If the treatment combination of the experimental arm demonstrates an acceptable safety profile in the Safety Run-In (1 or fewer patient experiences a protocol-defined DLT), randomized enrollment into the trial will begin.

A total of 54 patients will be enrolled in this study; 6 patients in the Safety Run-In and 48 patients in the randomized portion of the study. The expected accrual is 4 patients per month total at approximately 8 CITN sites. A study with 48 randomly assigned patients (1:1 randomization) will meet the following statistical parameters: H_{null} = 14.8%; H_{alt} = 45%; one-sided alpha of 0.10; power 88%.

The interim futility analysis will be conducted when 24 randomized patients have their first disease assessment and survival information. The futility analysis is based on an O'Brien-Fleming boundary, and the futility boundary will be considered to be crossed when the difference of ORR in the experimental arm – ORR in the control arm is less than -0.0063. Under the null hypothesis, the probability of crossing the futility boundary is 48.2%.

Safety Population: All patients who receive at least 1 dose of the investigational regimen will be considered evaluable for safety and included in the overall safety analysis. For the Safety Run-in phase, in the absence of a DLT, patients must complete the full 28-day DLT window period to be considered evaluable for DLTs. Patients who discontinue from the study before the completion of the full 28-day DLT window for reasons other than the occurrence of a DLT (*e.g.,* withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

Efficacy Population: The efficacy analysis will be conducted on all randomized patients, based upon the intent-to-treat population.

PLANNED ENROLLMENT REPORT

	Ethnic Categories		
Racial Categories	**Not Hispanic or Latino**	**Hispanic or Latino**	**Totals**

	Female	Male	Female	Male	
American Indian/ Alaska Native	1	2			3
Asian	1	4		1	6
Native Hawaiian or Other Pacific Islander	1	1		1	3
Black or African American	2	8	1	3	14
White	3	17	2	6	28
More Than One Race					
Total	8	32	3	11	54

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13.4 Stratification Factors

Patients will be randomly assigned to either the control arm (Atezolizumab monotherapy) or experimental arm (Atezolizumab + CYT107) of the trial. The randomization will not be stratified.

The PD-L1 level is considered an important predictive variable. Thus, a stratified analysis by PD-L1 level is considered for analysis as a secondary objective.

13.5 Analysis of Secondary Endpoints

13.5.1 *Secondary Objectives*

Statistical analyses will be conducted for the following secondary objectives:

- The CBR, PFS, DOR, as measured by RECIST v1.1 and irRC, and OS.
- The CBR, PFS, DOR, and OS in patients stratified by PD-L1 expression levels in the tumor microenvironment, as assayed by Genentech.

The CBR is defined as the percentage of patients with advanced or metastatic cancer who have achieved CR, PR, and SD to a therapeutic intervention in clinical trials of anticancer agents. A two-sided test for a difference in proportions will be conducted to compare the CBR in the experimental arm to the CBR in the control arm. A two-sided significance level of 0.05 will be considered for the test.

The PFS, DOR, and OS will be summarized using Kaplan-Meier estimates. Long-rank tests will be conducted for OS and PFS to compare between the 2 arms. A one-sided significance level of 0.10 will be considered.

13.5.2 *Exploratory Endpoints*

Statistical analyses will be conducted to determine the immune correlates of the clinical activity of the investigational treatment combination.

The endpoints will include the evaluation of the effect of the investigation treatment combination on the immune-bias of the tumor microenvironment, based upon baseline and post-baseline tumor biopsy comparisons of:

- Number, distribution, and phenotype of tumor-infiltrating cells
- PD-L1 expression
- Expression of Interferon γ (IFNγ) and associated proinflammatory gene expression in the tumor microenvironment

Analyses may be also performed to explore the effect of the investigational treatment combination on the number and phenotype of tumor-specific T cells in the peripheral blood, investigate for evidence that the investigational treatment combination increases the exposure of bladder cancer-specific antigens (*e.g.,* Cancer/Testis Antigens or neoantigens), and investigate changes in tumor microenvironment that correlate with response or provide information on potential actionable causes for lack of clinical benefit.

The effect of CYT107 on the infiltrating T cells will be assessed using the paired baseline and post-baseline results of the patients. The patient's baseline result will serve as the control for the comparison. Log-transformed values will be considered for the comparison of the number of infiltrating T cells.

It was established that the CYT107 dose regimen can double the number of peripheral blood T cells. There had been no prior information on the effect of CYT107 on infiltrating T cells. Assuming the CYT107 dose regimen also similarly doubles the number of infiltrating T cells, standard error of the effect size in the log scale (i.e. log(post-baseline) – log(baseline)) being 1, and a two-sided alpha of 0.10, a sample size of 13 paired samples will have 80% power to detect any difference between baseline and post-baseline.

13.6 Reporting and Exclusions

13.6.1 *Evaluation of Toxicity*

All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab and/or CYT107.

13.6.2 *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 possible 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. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should 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 (early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also 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 CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP-sponsored research protocol, then the guidelines below must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of AE to ensure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Before the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for ensuring that IRB approval has been obtained at each participating site before the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are 2 options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of 2 ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, *etc.*, available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number, and email address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C IMMUNE-RELATED RESPONSE CRITERIA

Introduction

Increasing clinical experience indicates that traditional response criteria (*e.g.,* Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1][Eisenhauer 2009] and World Health Organization [WHO]) may not be sufficient to fully characterize activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, CR, PR, or SD has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long term effect on the target disease must also be captured. The immune-related response criteria (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (*i.e.,* ipilimumab) [Wolchok 2009]. (***Note:*** The irRC only index and measurable new lesions are taken into account.)

Glossary

Term	Definition
SPD	sum of the products of the 2 largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

Baseline Assessment Using irRC

Step 1. Identify the index lesions (5 lesions per organ, up to 10 visceral lesions and 5 cutaneous lesions).

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

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

Post-Baseline Assessments Using irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions (≥5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions).

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

Step 4. Calculate the tumor burden:

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

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

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

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

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

Determination of irBOR

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

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

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

APPENDIX D DOSE ADJUSTMENT FOR OBESE PATIENT

Obesity is defined as a BMI >30 (NHLBI Class 1 Obesity)

In order to determine the proper dose for patients classified as obese, an adjusted body weight is calculated. The following steps are provided to assist with the process:

BMI Chart

BMI	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Ht	Wt (lbs)													
4'10"	91	96	100	105	110	115	119	124	129	134	138	143	167	191
4'11"	94	99	104	109	114	119	124	128	133	138	143	148	173	198
5'0"	97	102	107	112	118	123	128	133	138	143	148	153	179	204
5'1"	100	106	111	116	122	127	132	137	143	148	153	158	185	211
5'2"	104	109	115	120	126	131	136	142	147	153	158	164	191	218
5'3"	107	113	118	124	130	135	141	146	152	158	163	169	197	225
5'4"	110	116	122	128	134	140	145	151	157	163	169	174	204	232
5'5"	114	120	126	132	138	144	150	156	162	168	174	180	210	240
5'6"	118	124	130	136	142	148	155	161	167	173	179	186	216	247
5'7"	121	127	134	140	146	153	159	166	172	178	185	191	223	255
5'8"	125	131	138	144	151	158	164	171	177	184	190	197	230	262
5'9"	128	135	142	149	155	162	169	176	182	189	196	203	236	270
5'10"	132	139	146	153	160	167	174	181	188	195	202	207	243	278
5'11"	136	143	150	157	165	172	179	186	193	200	208	215	250	286
6'0"	140	147	154	162	169	177	184	191	199	206	213	221	258	294
6'1"	144	151	159	166	174	182	189	197	204	212	219	227	265	302
6'2"	148	155	163	171	179	186	194	202	210	218	225	233	272	311
6'3"	152	160	168	176	184	192	200	208	216	224	232	240	279	319
6.4"	156	164	172	180	189	197	205	213	221	230	238	246	287	328

If BMI >30, proceed with the following steps:

- **Determine Ideal Weight (1 kg = 2.2 lbs)**

  Males: 50 kg + (2.3 kg/inch over 5 feet)

  Females: 45.5 kg + (2.3 kg/inch over 5 feet)
  (Patients less than 5 feet: subtract 2.3 kg/inch)

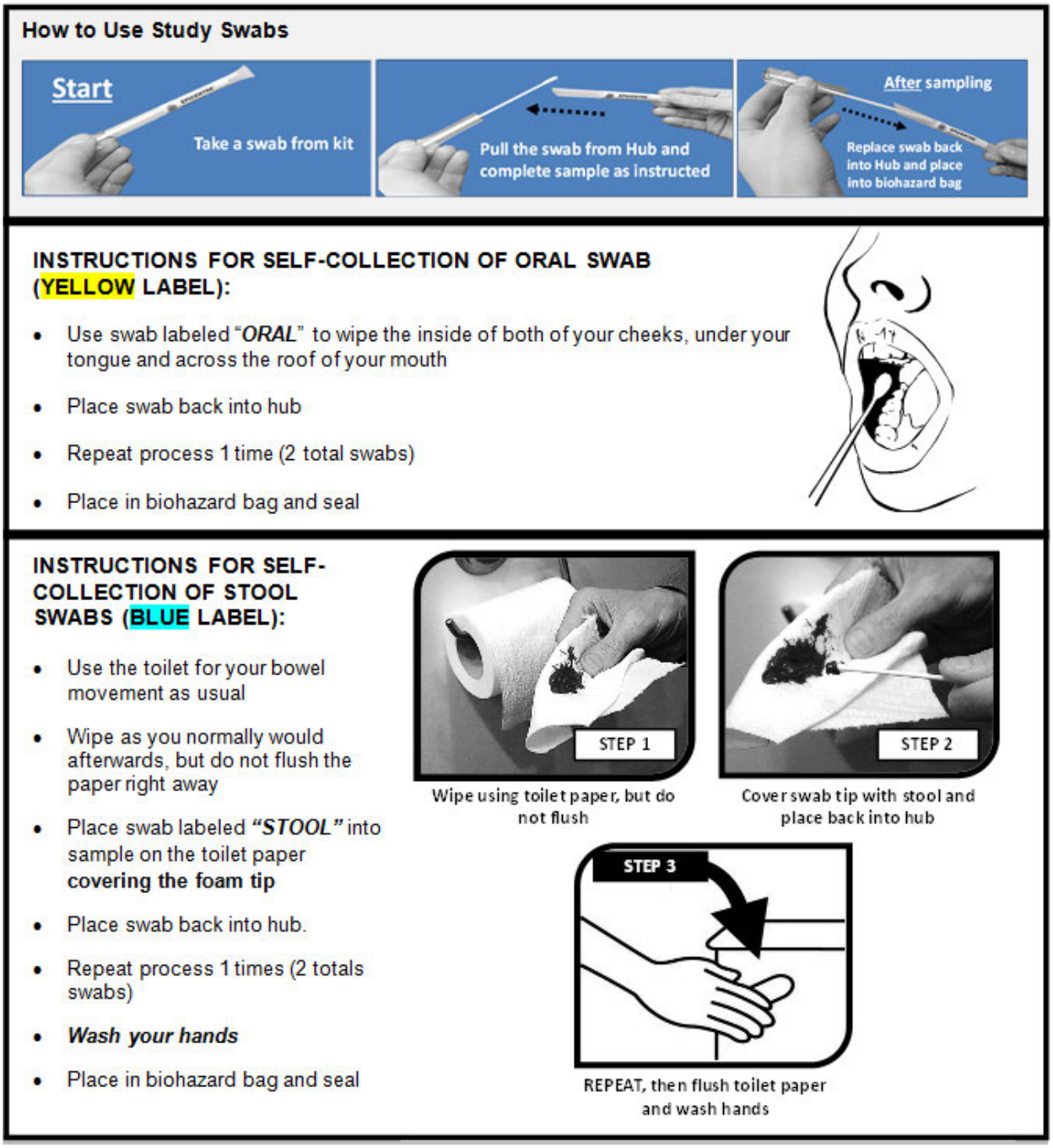
- **Determine Adjusted Body Weight:**

  Ideal Weight + 0.25 (actual weight – ideal weight) = Adjusted Body Weight

APPENDIX E MICROBIOME SAMPLE COLLECTION

Patient Instructions: The clinical research team will provide you with fecal swab/storage devices and the instructions sheet at the screening visit and at the Cycle 3 (Week 8) visit.

1. Collect the sample at home using the standardized fecal swab/storage devices provided.
2. Store the sample in the freezer at home.
3. Return the sample to the clinical research team ***at your next study visit.***



APPENDIX F ABBREVIATIONS LIST

AE	adverse event
AP	Associate Plus
BAL	bronchoscopic alveolar lavage
CAEPR	Comprehensive Adverse Events and Potential Risks
CBR	clinical benefit rate
CDUS	Clinical Data Update System
CIML	CITN Immune Monitoring Laboratory
CITN	Cancer Immunotherapy Trials Network
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COSC	Central Operating and Statistical Center
CR	complete response
CRF	case report form
CRS	clinical research site
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Monitoring Service
CTSU	Cancer Trials Support Unit
DLT	dose-limiting toxicities
DMC	data monitoring committee
DOR	duration of response
FDA	Food and Drug Administration
FDF	financial disclosure form
FFPE	formalin-fixed paraffin-embedded
FWA	Federal Wide Assurance
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

HSCT	hematopoietic stem cell transplantation
IAM	Identity and Access Management
ICF	informed consent form
IDF	Investigator Data Form
IME	important medical events
IRB	Institutional Review Board
LCMV	lymphocytic choriomeningitis virus
LPO	Lead Protocol Organization
MDSC	myeloid-derived suppressor cells
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer (cells)
OAOP	Online Agent Order Processing
OHRP	Office for Human Research Protection
OPEN	Oncology Patient Enrollment Network
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PI	principal investigator
PIO	Protocol and Information Office
PMB	Pharmaceutical Management Branch
PR	partial response
PSA	prostate-specific antigen
RCC	renal cell carcinoma
RCR	Registration and Credential Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RSS	Regulatory Support System
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class

SPEER	Specific Protocol Exceptions to Expedited Reporting
TCR	T-cell receptor
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
TSH	thyroid-stimulating hormone
UBC	urothelial bladder cancer
UC	urothelial carcinoma
ULN	upper limit of normal
WGS	whole genome shotgun