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TITLE: Rapid Analysis and Response Evaluation of Combination Anti-neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 3 Tiragolumab + Atezolizumab

Abbreviated Title: RARE 3 Tiragolumab Atezolizumab

Corresponding Organization: LAO-NCI/National Cancer Institute LAO
National Cancer Institute
10 Center Drive, 12N226
Bethesda, MD 20892

Principal Investigator: Jibran Ahmed, MD, DCTD
Developmental Therapeutics Clinic, NCI
31 Center Drive
Bldg 31 Room [redacted]
Bethesda, MD 20892
Phone: [redacted]
Fax: [redacted]
[redacted]

Participating Organizations:

LAO-NCI / National Cancer Institute LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO

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Responsible Research Nurse: [redacted] RN, DCTD/NCI
Bldg 10/RM [redacted]
Bethesda, MD 20892
Phone: [redacted]
Fax: [redacted]

Statistician: [redacted] PhD, BRB/DCTD/NCI
9609 Medical Center Drive
Rockville, MD 20850
Phone: [redacted]
Fax: [redacted]

NCI-Supplied Agents: Atezolizumab (MPDL3280A) (NSC 783608)
Tiragolumab (RO7092284) (NSC 827799)

IND #: **Atezolizumab and Tiragolumab:** [redacted]

IND Sponsor: DCTD, NCI

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PRÉCIS

Background:

- Rare tumors constitute a heterogeneous group of malignancies associated with limited treatment options and poor outcomes.
- Therapy combinations are being tested in patients with rare cancers in a series of connected Phase 2 clinical trials (*Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors [RARE CANCER]*); responses may trigger further evaluation of a treatment in that rare cancer type to further evaluate response rate and mechanism-of-action. Patients who progress will be offered another RARE CANCER trial.

Primary objective:

- Determine the proportion of activated CD8+ T cells at baseline and after treatment (cycle 3, day 1) with atezolizumab and tiragolumab.

Secondary objectives:

- Determine the objective response rate (ORR) of patients with advanced rare cancers to the combination of atezolizumab and tiragolumab using RECIST v 1.1 and iRECIST guidelines.
- Measure progression-free survival (PFS) time (time frame: baseline until disease progression, death, loss to follow-up, initiation of another anti-cancer treatment, withdrawal of consent, or study termination).
- Measure the proportion of patients with a clinically promising increase in CD8+ T cell infiltration following treatment with atezolizumab and tiragolumab.

Eligibility:

- A histologically confirmed solid tumor meeting the RARECARE definition of rare cancer that has progressed on standard therapy known to prolong survival or for which no standard treatment options exist.
- Patients who are eligible for the Pediatric Early Phase Clinical Trials Network (PEP-CTN) study will be excluded.
- Age ≥18 years.
- No major surgery, radiation, or chemotherapy within 2 weeks prior to entering the study (6 weeks for nitrosoureas and mitomycin C) or 5 half-lives of the agent, whichever is shorter; toxicity from prior treatment must have recovered to eligibility levels.
- Prior immune checkpoint inhibitor (excepting prior anti-TIGIT) therapy is allowed.
- Adequate organ function; performance status ECOG ≤2.

Study Design:

- Patients will receive atezolizumab 1200 mg and tiragolumab 600 mg IV on day 1 of a 21-day cycle.
- Mandatory tumor biopsies will be collected at baseline and on cycle 3 day 1 (±3 days) for pharmacodynamic assessment. If possible, at the discretion of the PI and interventional radiologist, the same tumor lesion will be biopsied at baseline and after treatment (C3D1).

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- Mandatory blood samples will be collected at baseline and Day 1 of every cycle for cfDNA and CTC analysis for the evaluation of therapy-resistant mechanisms in the tumor.
- The accrual ceiling is 15 patients.

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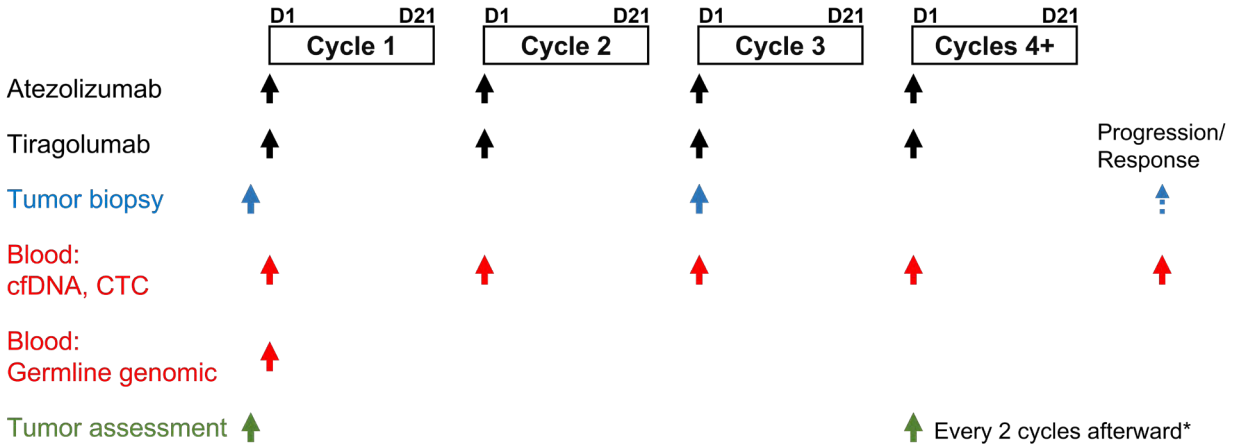
SCHEMA



Patients will receive atezolizumab IV (1200 mg) and tiragolumab IV (600 mg) on day 1 only of every 21 day-cycle.

Research tumor biopsies (mandatory†) will be collected from patients at baseline and prior to cycle 3 day 1 (±3 days) for the assessment of pharmacodynamic endpoints. One optional tumor biopsy may also be collected at time of disease progression or response (according to RECIST criteria).

Research blood sample collection will be mandatory for all patients to evaluate emerging therapy-resistance mechanisms in the tumor. Blood samples will be collected at baseline; every cycle on day 1; and at time of progression or response for cfDNA and CTC analysis. Baseline for germline genomic analysis will be performed from an aliquot of the blood sample collected for cfDNA analysis.

Patients will undergo a CT scan at baseline, on cycle 4 day 1, and repeat scans will be performed every 2 cycles afterward*.

†Mandatory for patients in which biopsies are deemed safe and feasible. Patients that cannot be safely biopsied may be considered for the study upon discussion with Principal Investigator.

*CT scans will be repeated every 3 cycles for patients on study for more than 1 year and every 4 cycles for patients on study more than 3 years.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Determine the proportion of activated CD8+ T cells at baseline and after treatment with atezolizumab and tiragolumab.

1.2 Secondary Objectives

1.2.1 Determine the objective response rate (ORR) of patients with advanced rare cancers to the combination of atezolizumab and tiragolumab using RECIST v 1.1 and iRECIST guidelines.

1.2.2 Measure progression-free survival (PFS) time (time frame: baseline until disease progression, death, loss to follow-up, initiation of another anti-cancer treatment, withdrawal of consent, or study termination).

1.2.3 Measure the proportion of patients with a clinically promising increase in CD8+ T cell infiltration following treatment with atezolizumab and tiragolumab.

1.3 Exploratory objectives

1.3.1 Investigate immune activation markers and the immune composition (Treg, NK, B-cells, macrophages, MDSC, TMB, MSI) in TME before and after study treatment.

1.3.2 Measure TCR signaling in tumor-infiltrating T cells in the TME as well as in circulating T cells in blood before and after study treatment using multiplex immunofluorescence assays (IFAs)—developed by the NCI-Frederick Pharmacodynamic Assay Development & Implementation Section (PADIS)—and use these measurements to evaluate the relationship between TCR signaling in circulating T cells and TME.

1.3.3 Evaluate potential associations between atezolizumab and tiragolumab activity and tumor genomic alterations, genomic expression, or TMB as determined from genomic analysis of biopsy samples.

1.3.4 Evaluate genomic alterations in cell free DNA (cfDNA) and their potential association with therapy response or resistance.

1.3.5 Evaluate the pharmacodynamic effects of the treatment on biomarkers of cell death and epithelial-to-mesenchymal transition (EMT) in tumor tissue and circulating tumor cells (CTCs).

1.3.6 Evaluate markers of immune response and the presence of tertiary lymphoid structures (TLS) in TME at baseline and following atezolizumab plus tiragolumab therapy.

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2. BACKGROUND

2.1 Rare tumors

Rare cancers, defined as malignancies with an annual incidence of less than 6 per 100,000 people according to RARECARE and NCI consensus [1], account for approximately 20% of newly diagnosed cancers in the United States. This heterogenous group of malignancies is associated with poor overall prognosis due to frequently delayed diagnosis and limited treatment options available for the afflicted patients [1-5]. The 5-year survival rate is 55% in males and 60% in females, significantly lower than the rates reported for more common cancers [4]. Despite incentives provided to pharmaceutical companies via the Orphan Drug Act of 1983 to develop new therapeutic agents for rare diseases, patients with rare cancers are often underrepresented in clinical trials.

The feasibility of accruing patients harboring rare cancers was demonstrated in the SWOG 1609 study (DART; NCT02834013), a phase 2 basket trial that tested dual immune checkpoint blockade with anti–PD1 (nivolumab) and anti–CTLA-4 (ipilimumab) antibodies in patients with rare cancers selected from the RARECARE list (Appendix C). The response rate in patients with high-grade neuroendocrine carcinomas was reported to be 26% and the clinical benefit rate (defined as the percentage of patients with stable disease for ≥6 months, partial response [PR], or complete response [CR]) was 32% [6]. The results from this trial highlight the importance of testing dual immune checkpoint inhibitor (ICI) therapies in rare cancers.

This proposed trial, termed RARE3, will evaluate the proportion of patients ages 18 and older with rare cancers who have significant changes in the percentage of activated tumor infiltrating CD8+ T cells following the combination treatment of 2 ICIs: atezolizumab (anti–PD-L1) and tiragolumab (anti–TIGIT). This will be the third clinical trial in the *Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors (RARE CANCER)* study series, preceded by RARE1 (testing the nilotinib and paclitaxel combination; NCT04449549; non-ETCTN study currently accruing at NCI), and RARE2 (testing the talazoparib and temozolomide combination; NCT05142241; non-ETCTN study currently accruing at NCI). The series is designed so that patients who do not respond to treatment on a particular RARE study can move to another available trial in this series. The proposed trial will accrue patients who have rare cancers including those denoted in DART, rare sarcomas or others considered to meet the definition of a rare cancer by the PI (see Appendix C).

2.1.1 Antitumor immunity and immune evasion in cancer

Immunotherapies enhance anti-tumor immune responses that can arise spontaneously in patients [7]. Mounting effective antitumor immunity requires 3 steps: 1) dendritic cells (DCs) are exposed to tumor antigens while also receiving a maturation signal; 2) activated tumor-antigen-loaded DCs migrate to lymphoid organs where they can stimulate CD8+ T cells and trigger natural killer (NK) cell responses; 3) cancer-specific T cells must enter the tumor bed [7, 8]. Tumor antigens that can trigger an immune response include overexpressed non-mutated proteins, and mutated tumor-specific antigens (TSAs) (e.g.: gene fusions, single nucleotide variants). TSAs can be caused by mutagen exposures, DNA-replication errors, high microsatellite instability (MSI-H), etc. [9]. Although a high tumor mutational burden (TMB)

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should be associated with a higher number of TSAs that can trigger an anti-tumor immune response, the predictive value of the TMB as a marker for cancer immunotherapy remains unclear [10, 11].

Cancer cells can evade immune recognition by downregulating tumor antigens or MHC-I molecules, or by taking advantage of negative feedback mechanisms such as: secreting inhibitory cytokines (IL-10, TGF-β), attracting inhibitory cell types (regulatory T cells [Tregs], tumor associated macrophages [TAMs]), releasing metabolic modulators, and displaying inhibitory ligands (PD-L1, CD155, etc.) on cancer and other tumor microenvironment (TME) cells [7, 12]. CD8+ T cells are key anti-tumor effectors that kill tumor cells with cytotoxic molecules, and produce IFNγ to increase the expression of MHC-I antigens by tumor cells [13]. Importantly, certain tumor immune evasive mechanisms can make neoplastic cells vulnerable to different anti-tumor effectors; for e.g.: MHC-I deficient tumor cells are refractory to CD8+ T cell-mediated immunity, but trigger NK-mediated cytotoxicity [14].

2.1.1.1 T-cell receptor signaling

T cell activation requires simultaneous engagement of the T cell receptor (TCR), CD4 or CD8 co-receptors, and co-stimulatory molecules (e.g. CD28) [14]. The TCR is a heterodimer, lacking inherent signal transducing activity, that associates non-covalently with multiple signal transducing subunits: CD3γ, CD3δ, CD3ε and a CD3ζ homodimer. CD3 chains contain immunoreceptor tyrosine-based activation motif(s) (ITAM) [15].

The SRC family protein tyrosine kinase LCK is then recruited to the TCR by CD4 or CD8 co-receptors. LCK phosphorylates ITAMs in the CD3 chains, enabling the docking and activation of zeta-chain-associated protein kinase-70 (ZAP70) [16]. LCK kinase activity is controlled by phosphorylation of tyrosine Y394 (which stabilizes the active conformation of the catalytic domain) and Y505 (which renders the kinase inactive) [15]. Phosphorylation of ZAP70 on Y493 by LCK activates the ZAP70 kinase activity. LCK can also phosphorylate ZAP70 at Y126, leading to release of active ZAP70 and TCR signal propagation [15]. ZAP70 then phosphorylates the transmembrane adaptor protein linker for activation of T cells (LAT). LAT phosphorylation leads to the recruitment of multiple adaptors and effector molecules, which ultimately results in T cell proliferation, migration, cytokine production and other effector functions [15].

Several inhibitory receptors control T cell activation by inhibiting early TCR signaling to avoid T cell hyperactivation and damage caused by chronic antigen exposure [15]. Inhibitory receptors lack intrinsic enzymatic activity but have cytoplasmic tails with immunoreceptor tyrosine-based inhibitory motifs (ITIMs) or an immunoreceptor tyrosine-based switch motif (ITSM) that are phosphorylated upon agonist ligation and TCR signaling. These phosphorylated domains serve as docking sites for tyrosine phosphatases such as SHP-1 and SHP-2 that signal through inhibitory receptors such as programmed cell death protein 1 (PD-1). Following PD-1 activation, SHP-2, and to a lesser extent SHP-1, dephosphorylate ZAP70 and downregulate T cell activation [17]. Zap70 is therefore the integration point between stimulatory (TCR) and inhibitory (immune checkpoint) signaling.

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2.2 CTEP IND Agents

2.2.1 Atezolizumab

Atezolizumab (Tecentriq™) is a human monoclonal antibody directed against programmed death-ligand 1 (PD-L1) designed to reinvigorate anti-tumor immunity. Atezolizumab targets immune cells or tumor cells and prevents interaction with either programmed death-1 (PD-1) receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1:PD-1 and PDL1: B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function [18, 19]. In October 2021 Tecentriq™ was approved for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (on ≥ 1% of tumor cells). Previous approvals have been granted for atezolizumab (as monotherapy or in combination) for advanced bladder cancer, advanced melanoma, liver cancer and extensive stage small cell lung cancer.

Atezolizumab consists of two heavy chains (448 amino acids each) and two light chains (214 amino acids each). The fragment crystallizable (Fc) effector function of this antibody was eliminated via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, yielding a non-glycosylated antibody with minimal binding to Fc receptors that eliminates depletion of cells expressing PD-L1.

Mechanism of Action

PD-L1 is a glycoprotein in the B7 ligand family and is commonly expressed by 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 [20-23]. PD-L1's receptor PD-1 is expressed on activated T cells, and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer [22]. Under normal circumstances, the PD-1/PD-L1 pathway restrains the hyperactivation of immune cells and prevents autoimmune diseases, as PD-L1 binding to PD-1 can diminish T cell-mediated immune surveillance, resulting in an absence of immunoreaction and ultimately apoptosis of T cells [24]. In cancer however, overexpression of PD-L1 on tumor cells and tumor-infiltrating immune cells, such as macrophages and dendritic cells, impedes anti-tumor immunity and contributes to immune evasion [25]. Given the inhibitory effects of PD-L1 signaling on T cell proliferation and activity, targeted interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. Blockade of PD-L1 with monoclonal antibodies results in strong and durable anti-tumor effects in patients [26, 27]. Importantly, PD-L1 expression in tumor-associated immune cells corelates with a higher probability of clinical response to anti-PD-L1 therapy [28, 29]; however, PD-L1 expression levels in tumor tissue is not the sole predictor of response to anti–PD-L1/1 therapy [30]. Collectively, these data establish the PD-L1/PD-1 pathway as a promising therapeutic target in patients with advanced tumors.

Given the inhibitory effects of PD-L1 signaling on T cell proliferation and activity, targeted interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathways represent an attractive strategy to reinvigorate tumor-specific T-cell immunity. The other known ligand of PD-1, programmed death-ligand 2 (PD-L2), is primarily expressed in normal tissues such as the lung. As a result,

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targeting tumor-overexpressed PD-L1 is a more promising strategy than targeting PD-1, as it preserves the immune homeostatic PD-L2:PD-1 interaction in normal tissues while dually inhibiting the PD-L1:PD-1 and PD-L1:B7.1 pathways to enhance anti-tumor T cell immunity. PD-L1/PD-1 pathway is therefore a promising new therapeutic target in patients with advanced tumors.

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. Please refer to the Investigator's Brochure for details on the nonclinical studies.

Summary of Clinical Experience

As of May 2021, current clinical studies of atezolizumab include 116 company-sponsored studies with atezolizumab as a single agent or in combination with other therapies. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure Version 18 (July 2021).

Clinical PK and Immunogenicity

Atezolizumab pharmacokinetics and other data have been analyzed from a number of company-sponsored monotherapy studies (Investigator's Brochure, 2021). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including the fixed dose of 1200 mg administered every 3 weeks. On the basis of a population pharmacokinetic analysis that included 472 patients (Studies PCD4989g and JO28944) in the dose range of 1 mg/kg to 20 mg/kg, the typical population clearance (CL) was 0.20 L/day, the volume of distribution at steady state (V_{ss}) was 6.9 L, and the terminal half-life ($t_{1/2}$) was 27 days. The population PK analysis suggested that steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the concentration-time curve (AUC), maximum concentration (C_{max}), and trough concentration (C_{min}) was 1.91, 1.46, and 2.75-fold, respectively, following intravenous administration of 1200 mg atezolizumab every 3 weeks. Atezolizumab pharmacokinetics after combination administrations with other anti-cancer agents were comparable to those following atezolizumab monotherapy administrations.

ADAs to atezolizumab have been observed at ≤ 1 mg/kg to 20 mg/kg and at 1200 mg (Investigator's Brochure, 2021). ADA status appears to have no clinically relevant impact on pharmacokinetics, safety, or efficacy.

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Clinical Safety Summary

As of May 17, 2021, atezolizumab has been administered (alone or in combination with other agents) to > 27,000 patients with solid tumors and hematologic malignancies (Investigator's Brochure, 2021). Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated with a manageable adverse event profile. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events (AEs) have been determined.

Among 3178 patients treated with single-agent atezolizumab for whom pooled safety data are available, the most commonly reported AEs (≥ 10%) include fatigue, decreased appetite, nausea, cough, dyspnea, constipation, pyrexia, diarrhea, anemia, back pain, vomiting, asthenia, arthralgia, pruritus, rash, headache, urinary tract infection, and peripheral edema (Investigator's Brochure, 2021). The adverse events (AEs) observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of the individual study treatment.

As of July 2021, pooled safety data for atezolizumab monotherapy are available for 3178 treated patients in 8 studies: IMvigor210, IMvigor211, OAK, BIRCH, POPLAR, FIR, IMmotion150, and PCD4989g (Investigator's Brochure, 2021). Over 97% of these patients received atezolizumab at a dose of 1200 mg every 3 weeks, and the remaining patients, from study PCD4989g, received atezolizumab at doses in the range of 1–20 mg/kg every 3 weeks. The median treatment duration range was 3.5 months (range 0–53). Of the 3178 patients, 3050 patients (96%) reported at least one AE of any grade, 1479 patients (46.5%) experienced at least one grade 3 or 4 AE, and 122 patients (3.8%) experienced grade 5 AE. Treatment-related AEs were reported in 68.2% of patients, with the most common events (≥ 20%) being fatigue, decreased appetite, nausea, cough, constipation, dyspnea, and pyrexia.

The incidence of serious adverse events (SAEs) in the overall pooled population was 41.2% (Investigator's Brochure, 2021). The most common SAEs were pneumonia (3.1%), dyspnea (2.8%), pyrexia (2.5%), urinary tract (1.9%) and pleural effusion, pulmonary embolism, and sepsis (1.3%). In the overall pooled population, 7.1% of patients experienced an AE that led to withdrawal of study treatment; most common AEs leading to withdrawal of treatment were pneumonitis, pneumonia, death, sepsis, septic shock, dyspnea, and increased AST.

Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program (Investigator's Brochure, 2021). These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness. To date, immune-related adverse events associated with atezolizumab include severe cutaneous AEs, hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis.

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Pericardial and pleural involvement with associated effusions is common in patients with cancer and has the theoretical potential to be exacerbated by inflammation associated with antitumor immunity following PD-L1 blockade. Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.
For further details, see the most recent Atezolizumab Investigator's Brochure.

Clinical Efficacy Summary

Efficacy data available as of July 2021 suggest that treatment with atezolizumab as a single agent or in combination with other therapeutic agents results in anti-tumor activity across a range of tumor types, across lines of therapy, and across PD-L1 expression subgroups (Investigator's Brochure 2021).

Patients with multiple tumor types were included in study PCD4989g, with the largest cohorts consisting of patients with NSCLC, RCC, and UC (Investigator's Brochure, 2017). 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. Objective responses were recorded for 20 of 88 (22.7%) response-evaluable patients with NSCLC, including responses in squamous and non-squamous patients. The median duration of survival follow-up at the time of the data cut-off (December 2, 2014) was 22.5 months. At that timepoint, the median duration of all responders was 17.3 months, with 40% (8 of 20) of responders having an ongoing response.

Analyses of tumor cells and tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for study PCD4989g, including expansion cohorts of patients with NSCLC (88 efficacy-evaluable patients), UC (87 efficacy-evaluable patients), and RCC (62 efficacy-evaluable patients) [19, 31] (Investigator's Brochure, 2017). Preliminary results suggest that PD-L1 expression in tumor-infiltrating immune cells is likely to be associated with response to atezolizumab. An objective response rate (ORR) of 43% (13 of 30 patients, including 2 complete responses) was observed in UC patients with tumor-infiltrating immune cells with PD-L1 immunohistochemistry (IHC) scores of 2 or 3, whereas the ORR among IHC 0/1 UC patients was 11% (4 of 35) [31]. Response to atezolizumab in the UC cohort was associated with the tumor-infiltrating immune cell IHC scores (P=0.026) but not with tumor cell IHC scores (P=0.93). Similarly, a preliminary analysis of the NSCLC cohort (53 evaluable patients) and the total patient population (175 evaluable patients) of PCD4989g found that response was significantly associated with PD-L1 IHC score in tumor-infiltrating immune cells (P=0.015 in NSCLC, P=0.007 in all tumors) but not with IHC score in tumor cells (P=0.920 in NSCLC, P=0.079 in all tumors) [20]. Eighty-three percent of NSCLC patients with an IHC score of 3 (tumor-infiltrating immune cell) responded to treatment, whereas 43% of NSCLC patients with IHC 2 were limited to disease stabilization.

Extensive efficacy data are now available for 2504 patients with non-small cell lung cancer (NSCLC) enrolled in three studies (IMpower150, IMpower130, and IMpower132) of atezolizumab in a first-line (1L) setting in combination with a variety of other treatment regimens. These studies demonstrated statistically significant and clinically meaningful improvement in OS and PFS in patients with non-squamous NSCLC upon addition of

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atezolizumab to other treatment regimens (IMpower150 and IMpower130) and similar improvement in PFS (IMpower132) (Investigator's Brochure 2021). A total of 1213 patients with locally advanced or metastatic urothelial carcinoma were enrolled to the IMvigor130 phase 3, randomized, placebo-controlled study (Investigator's Brochure 2021). IMvigor130 reported a statistically significant and clinically meaningful improvement in PFS as assessed by the local investigator in the atezolizumab + chemotherapy arm relative to placebo + chemotherapy in the intention to treat population (stratified HR: 0.82; 95% CI: 0.70–0.96; P=0.007) at the time of primary analysis (31 May 2019). Median PFS was longer in the atezolizumab + chemotherapy arm (8.2 months [95% CI: 6.5–8.3]) compared with the placebo + chemotherapy arm (6.3 months [95% CI: 6.2–7.0]) (Investigator's Brochure 2021). A meta-analysis of 14 clinical trials with 3266 patients with various cancers performed by Tie *et* al [32] found that 6% patients reached CR and 16% PR. The pooled 6-month PFS rate and 1-year OS rate were 0.36 (95% CI: 0.31–0.41) and 0.55 (95% CI: 0.49–0.61), respectively. The median PFS varied from 1.5 to 6.1 months, and the median OS ranged from 5.9 to 28.9 months [32]. Available clinical data therefore indicate that atezolizumab, as monotherapy or in combination, has a considerable potential in treating various cancers.

2.2.2 Tiragolumab

Tiragolumab (also known as MTIG7192A) is a fully human IgG1 kappa monoclonal antibody that binds and inhibits the membrane protein T cell immunoreceptor with Ig and ITIM domains (TIGIT) yielding antineoplastic activity. Tiragolumab consists of two heavy chains (456 amino acid residues each) and two light chains (220 amino acid residues each). There are two N-linked glycosylation sites (asparagine 306) in the Fc domain.

Mechanism of Action

TIGIT is a member of the immunoglobulin (Ig) super family and has been implicated in tumor evasion of innate immunity and immunotherapy [33]. TIGIT is expressed on lymphocytes, including subsets of activated T cells, NK cells and in tumor-infiltrating immune cells [34-36]. TIGIT interacts primarily with CD155 (poliovirus receptor – PVR), to which it binds with a higher affinity than the competing co-stimulatory receptor CD226 (**Figure 1**) [37-39]. TIGIT therefore inhibits T cell and NK cell function, and plays a critical role in limiting adaptive and innate immunity [40]. TIGIT ligand CD155 is expressed on monocytes, DCs, fibroblasts and endothelial cells on both healthy tissues and in tumors, and it is also overexpressed on cancer cells in several malignancies, including colon cancer, lung adenocarcinoma, melanoma, pancreatic cancer, glioblastoma and hepatocellular carcinoma [41]. CD155 overexpression on tumor cells correlates with tumor progression and unfavorable prognosis [41]. In CD8+ T cells, TIGIT downregulates the expression of the TCRα chain and of other molecules in the TCR complex; TIGIT also prevents CD226 homodimerization and its co-stimulatory signaling. Agonistic TIGIT ligation on Tregs enhances their suppressive function and TIGIT+ Tregs secrete immunosuppressive IL-10 and fibrinogen-like protein 2 (FGL2) which suppresses effector T cell proliferation [41]. TIGIT+ NK cells display lower cytolytic activity compared to TIGIT- NK cells against CD155+ MHC-I negative melanoma cells [42].

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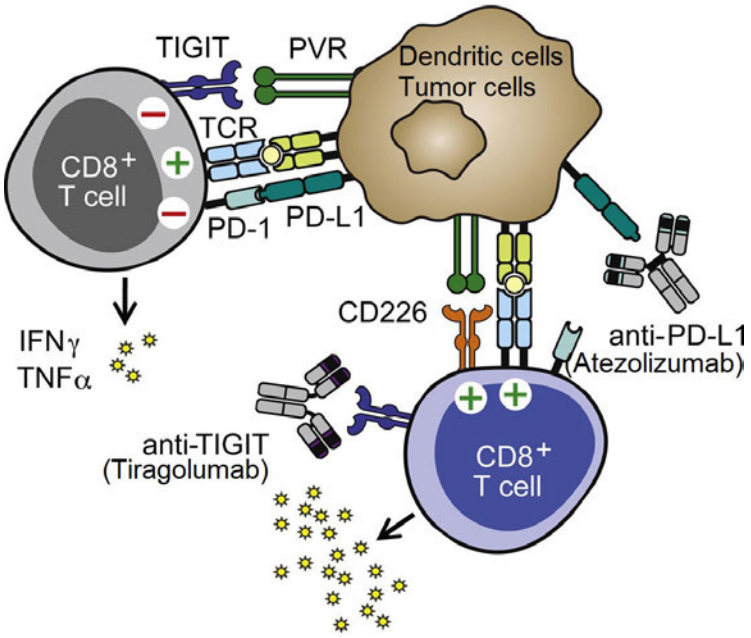

Figure 1: Mechanism of action for atezolizumab and tiragolumab

PD-L1 expressed on tumor cells or dendritic cells in the tumor microenvironment (TME) interacts with PD-1 on the surface of activated T cells and mediates T cell exhaustion. TIGIT disrupts T cell activation via interaction with CD155 (PVR), expressed on cells in the TME, and by inhibiting CD226 activation. Co-blockade of PD-L1 (with atezolizumab) and TIGIT (with tiragolumab) enhances CD8+ T cell effector function and leads to increased immune surveillance. Figure adapted from Johnson et al, [36].

TIGIT upregulation on tumor-infiltrating lymphocytes (TILs) has been detected in many malignancies including rare tumors [43-48]. Zhou and colleagues [47] performed transcriptomic analysis on 11 patients with osteosarcoma and reported that TIGIT was widely expressed on CD8+ T cells, FOXP3+ CD4+ T cells and NK cells infiltrating the TME; moreover, when peripheral blood CD3+ T cells from patients with high number of tumor TIGIT+CD3+T cells were treated with anti-TIGIT antibodies, the CD3+ T cells showed enhanced T cell effector function, suggesting a potential therapeutic role for TIGIT inhibition [47]. Upregulated TIGIT expression was also reported on T cells and NK cells in soft tissue sarcoma [48], in a subgroup of undifferentiated pleomorphic sarcoma samples [49] and in a case report in the tumor tissue from a patient with pulmonary clear cell sarcoma [46]. Anti-TIGIT antibodies showed anti-tumor activity *in vivo* as inhibition of TIGIT delayed tumor engraftment in syngeneic mouse models (MC38 colon carcinoma and B16 melanoma murine models) and prevented metastatic dissemination if TIGIT blockade was used before tumor establishment [50, 51]. Taken together, the data suggest TIGIT as a putative therapeutic target in patients with rare tumors. Moreover, TIGIT blockade synergizes with PD-L1/1 blockade and appears to overcome anti-PD1 resistance in tumors [41].

2.2.2.1 Atezolizumab and Tiragolumab Combination

Targeting single checkpoint proteins such as PD-1/PD-L1 may lead to upregulation of alternative immune checkpoint proteins that mediate acquired resistance [52]. Combination

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immunotherapies have been shown to improve disease outcomes for patients with treatment-refractory cancers [7].

Co-expression of PD-1 and TIGIT was reported to occur in both terminally differentiated and multipotent stem-like memory T cells with self-renewal ability, the latter of which have been increasingly recognized as attractive targets for cancer immunotherapy [53, 54]. Additionally, PD-1 and TIGIT are frequently co-expressed in TILs, peripheral memory T cells, and activated T cells in the TME, and a co-blockade resulted in enhanced activation of TILs compared to single blockade of either checkpoint [55].

Nonclinical Studies

As tiragolumab does not bind to mouse TIGIT, a murine reactive anti-TIGIT antibody (anti-muTIGIT) on a mouse IgG2a backbone (analogous to the human IgG1 backbone) was generated to evaluate the pharmacology and efficacy in the mouse syngeneic tumor model.

In vivo studies were conducted to assess the ability of anti-muTIGIT alone or in combination with an anti-PD-L1 antibody (anti-muPD-L1) to generate anti-tumor responses against established tumors in the CT26 syngeneic murine colon carcinoma tumor model.

Johnston and colleagues [36] demonstrated that PD-L1 and TIGIT co-blockade enhances CD8+ T cell-mediated tumor rejection in CT26 syngeneic colon carcinoma tumor mouse models; single agent treatment had only a marginal effect on tumor growth, whereas the combination resulted in more than 75% tumor regression by day 16 (**Figure 2**A) [36]. Tumor regression was also reflected in the increased overall survival of mice treated with both PD-L1 and TIGIT antibodies (**Figure 2**B). Interestingly, mice re-inoculated with the same CT26 tumor cell line following the combination treatment were able to clear tumors in the absence of further treatment; the same effect was not observed after the mice were subsequently inoculated with EMT6 breast carcinoma cells (**Figure 2**C) [36]. Furthermore, administration of anti-muTIGIT at dose levels between 1 and 10 mg/kg were equally effective at generating anti-tumor activity when given in combination with anti-muPD-L1. Importantly, co-inhibition of TIGIT and PD-L1 was well tolerated in the syngeneic tumor model and was not associated with any body weight loss or other observable adverse responses. These data support the notion that PD-L1 and TIGIT co-blockade establishes tumor antigen–specific immune memory through activation and amplification of stem-like memory T cells.

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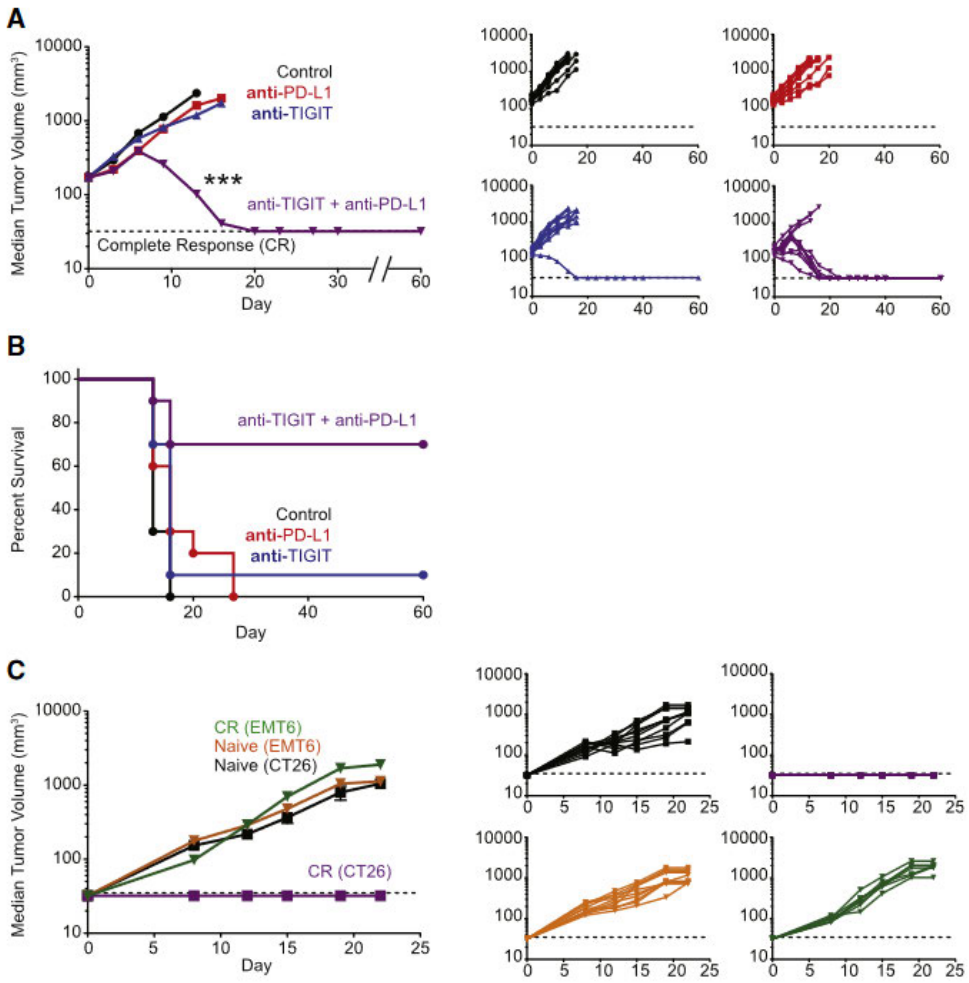

Figure 2: TIGIT and PD-L1 co-blockade improves tumor control in mice inoculated with CT26 syngeneic colon carcinoma cells. Following inoculation with the CT26 cells, mice were treated with isotype control (black), anti-PD-L1 + control (red), anti-TIGIT + control (blue), or the combination of anti-PD-L1 + anti-TIGIT (purple). **A)** Tumor volume change from baseline over time. Median tumor volumes (left graph) and individual tumor growth curves (right panel) indicate that the majority of mice receiving the combination experienced tumor regression, whereas only a single mouse achieved a complete response (CR) when treated with tiragolumab alone. **B)** Mouse survival over time. **C)** Approximately 60 days after initial inoculation, mice that reached CR after anti-TIGIT + anti-PD-L1 therapy were reinoculated with CT26 cells (left flanks) or inoculated with EMT6 breast carcinoma cells (mammary fat pads). Median (left) and individual (right) tumor volumes reveal that no tumor grew in CT26 re-inoculated mice. Figure is as shown in [36].

Clinical Pharmacokinetics

As of December 2019, a preliminary PK analysis was conducted based on available data from Study GO30103 (2–1200 mg tiragolumab administered every 3 weeks as a single agent [Phase Ia] and in combination with 1200 mg atezolizumab every 3 weeks [Phase Ib]). The PK of

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tiragolumab in combination with atezolizumab appeared to be consistent with the PK of tiragolumab administered as a single-agent and tiragolumab exposures increased approximately dose-proportionally following IV administration at doses ranging from 100 to 1200 mg administered every 3 weeks as monotherapy or in combination with 1200 mg atezolizumab every 3 weeks (Investigator's Brochure, April 2021). The estimated tiragolumab clearance is 0.28 L/day with a linear drug elimination half-life of approximately 15 days.

Clinical Pharmacodynamics

Biomarker samples from patients treated with tiragolumab as a single-agent or in combination with atezolizumab were evaluated for peripheral receptor occupancy, immune activation, and cytokine release in Study GO30103. From a dose of 30 mg tiragolumab up to the highest dose (1200 mg) tested, peripheral receptor occupancy on CD4+ T cells, CD8+ T cells, and NK cells was maintained at 100% for the entire duration of the study in all patients. A 2-fold increase in activated proliferating CD8+ T cells (CD8+HLA-DR+Ki-67+) and a trend of increased circulating interferon (IFN-γ) were observed 2 weeks after the first dose in patients treated with tiragolumab and atezolizumab.

Clinical Safety

As of December 2020, tiragolumab was administered to 235 safety-evaluable patients in both the phase 1a and phase 1b portions of study GO30103, including 42 patients who received single-agent tiragolumab in phase 1a portion of the study and 216 patients (of which 23 crossed over from the phase 1a portion of this study) received tiragolumab in combination with atezolizumab in the Phase 1b portion of the study (Investigator's Brochure, April 2021). In the phase 1a portion of the study, patients were treated with a median of 2 doses of tiragolumab (range: 1–20) and were on treatment for a median of 21.7 days (range: 0–400). Sixteen patients (38.1%) experienced a total of 28 grade ≥ 3 AEs regardless of attribution to study drug, and 3 patients (7.1%) experienced a total of 5 grade ≥ 3 AEs assessed to be related to tiragolumab. In the Phase 1b portion, patients were treated with a median of 4 doses of tiragolumab and atezolizumab (range: 1–63) for a median of 63.1 days (range: 0–1365). As of December 2020, 113 patients (52.3%) experienced a total of 240 Grade ≥ 3 AEs regardless of attribution to study drug. Twenty-one patients (12.4%) experienced a total of 27 Grade ≥ 3 AEs that were assessed to be related to the study drug(s) (tiragolumab and/or atezolizumab). A total of 17 SAEs were reported in 13 patients (31.0%) in phase 1a of study GO30103, including one grade 5 hepatic failure assessed as related to the study drug. In the phase 1b portion of the study, a total of 159 SAEs were reported in 92 patients (42.6%), of which 14 SAEs, reported in 10 (4.6%) patients, were considered to be related to study drug(s). These include grade 4 cardiac tamponade, amylase increase, lipase increase, and pneumonitis, grade 3 adrenal insufficiency, asthenia, diabetic ketoacidosis, hypertransaminasemia, and rhabdomyolysis. Importantly, no DLTs, have been reported for patients enrolled in either portion of the study.

As of June 2019, 66 out of 67 patients (98.5%) in the tiragolumab plus atezolizumab arm and 65 out of 68 patients (95.6%) in the placebo plus atezolizumab arm of the GO40290 (CITYSKAPE) trial reported at least one AE (Investigator's Brochure, April 2021). AEs that occurred at a higher frequency (≥ 5% difference between arms) in the tiragolumab plus atezolizumab arm were infusion related reactions (IRR) (28.4% vs. 10.3%), fatigue (22.4% vs. 13.2%), pruritus

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(19.4% vs. 11.8%), rash (19.4% vs. 8.8%), arthralgia (16.4% vs. 8.8%), peripheral oedema (10.4% vs. 4.4%), maculopapular rash (9.0% vs. 2.9%), pleural effusion (9.0% vs. 2.9%), back pain (9.0% vs. 2.9%). A total of 54 out of 67 patients (80.6%) in the tiragolumab plus atezolizumab arm experienced at least one AE that was assessed by the investigator to be related to the study treatments. Twenty-eight out of 67 patients (41.8%) in the tiragolumab plus atezolizumab arm experienced at least one grade ≥ 3 AE regardless of attribution to study treatments. Grade ≥ 3 AEs that occurred at a higher frequency (≥ 2% difference between arms) in the tiragolumab plus atezolizumab arm were pneumonia (9.0% vs. 4.4%), pleural effusion (6.0% vs.1.5%), increased lipase (6.0% vs. 2.9%) and hypokalemia (3.0% vs. 0%). A total of 10 out of 67 patients (14.9%) in the tiragolumab plus atezolizumab arm and 13 out of 68 patients (19.1%) in the placebo plus atezolizumab arm experienced at least one Grade ≥ 3 AE that was assessed by the investigator to be related to the study treatments. Only the event of lipase increased occurred in more than one patient (4 of 67; 6.0%) in the tiragolumab plus atezolizumab arm. Overall, a total of 30 SAEs were reported in 23 patients (34.3%) in the tiragolumab plus atezolizumab arm, and 38 SAEs were reported in 24 patients (35.3%) in the placebo plus atezolizumab arm, regardless of attribution to study treatments. A total of 9 SAEs reported in 7 patients (10.4%) in the tiragolumab plus atezolizumab arm, and 11 SAEs reported in 10 patients (14.7%) in the placebo plus atezolizumab arm, were considered by the investigator to be related to study treatments. In the tiragolumab plus atezolizumab arm, these include autoimmune nephritis, colitis, constipation, hepatitis, IRR, increased lipase, pyrexia, skin infection each in 1 patient. Of note, the SAE of infusion-related reaction occurred shortly after atezolizumab infusion prior to the patient receiving tiragolumab.

Clinical Efficacy

As of April 2021, there are 32 clinical studies registered at clinicaltrials.gov testing atezolizumab and tiragolumab combination, triplet combinations including atezolizumab and tiragolumab, or atezolizumab or tiragolumab combinations with other agents in different common solid malignancies. Several phase 1 and 2 trials have already examined the safety and/or preliminary activity of co-targeting PD-L1 and TIGIT.

In the first-in-human dose escalation phase 1a/b study of tiragolumab (GO30103), 190 patients (cutoff date: December 2019) with a variety of tumor types received treatment with escalating doses of tiragolumab (2-1200 mg) alone (phase 1a; n= 42) and in combination with 1200 mg atezolizumab (phase 1b; n = 171, including 23 phase 1a patients who crossed over) (NCT02794571). In the phase 1a portion of the study, no complete or partial responses were recorded as per RECIST v1.1; 8 out of 42 (19%) of patients had a best response of stable disease. In the Phase 1b portion of the study, a total of 27 out of 171 (15.7%) of patients had a response according to RECIST criteria; 4 patients (2.3%) achieved CR (tiragolumab levels: 400 and 600 mg in combination with 1200 mg atezolizumab) and 23 patients (13.4%) achieved PR (tiragolumab levels: 30 mg, 400 mg, and 600 mg in combination with 1200 mg atezolizumab). Stable disease was observed in 39 out of 171 (22.8%) patients at tiragolumab dose levels ranging from 2-1200 mg in combination with 1200 mg atezolizumab. The combination of tiragolumab and atezolizumab was therefore well-tolerated and had an acceptable safety profile across all dose levels; the combination treatment increased the percentage of patients achieving clinical response and also increased the number of activated proliferating CD8+ cells.

CITYSCAPE is a randomized phase 2 double-blind prospective trial that enrolled chemotherapy-

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naïve non-small cell lung cancer (NSCLC) patients with locally advanced or metastatic disease (NCT03563716). Patients were required to have PD-L1 tumor proportion score of ≥ 1% (defining PD-L1 positive expression [56]) and could not harbor either EGFR or ALK alterations. ORR and progression-free survival (PFS) were co-primary endpoints. A total of 135 patients were randomized to receive either tiragolumab 600 mg IV + atezolizumab 1200 mg IV Q3W (n=67), or placebo + atezolizumab 1200 mg IV Q3W (n=68) [57]. ORR in the double treatment arm was 31.3% (95% CI: 19.49-43.2) vs 16.2% (95% CI: 6.69-25.66) in the single treatment arm (odds ratio 2.57; 1.07 - 6.14). Median PFS in the combination treatment arm was 5.4 months (95% CI: 4.2-NE) vs 3.6 months (95% CI: 2.7-4.4) in the single treatment arm (HR 0.57) (**Figure 3**). ORR appeared to be primarily driven by high PD-L1 expression in the tumor (TPS >50%) (Investigator's Brochure, April 2020). Based on these results, the FDA has granted the tiragolumab and atezolizumab combination a breakthrough therapy designation (BTD) in metastatic NSCLC patients whose tumors express PD-L1 and do not harbor EGFR or ALK mutations.

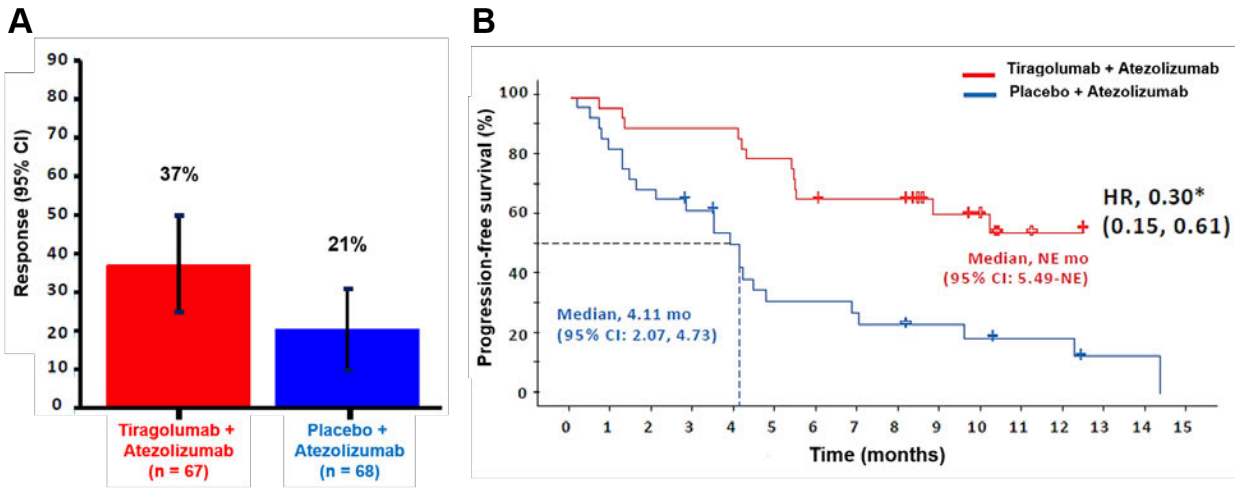

Figure 3: CITYSCAPE phase 2 randomized double-blind trial updated analysis with 10.9 months follow up. **A)** Overall response rate (ORR) in all 135 patients. **B)** Investigator assessed progression free survival (PFS). Proprietary data curtesy of Genentech.

However, the follow-up randomized phase 3 study SKYSCRAPER-01evaluating tiragolumab plus atezolizumab versus atezolizumab alone as first-line therapy for patients with PD-L1-high locally advanced or metastatic NSCLC did not meet its co-primary endpoint of PFS [58]. Similarly, the phase 3 randomized double-blind placebo-controlled study of atezolizumab + carboplatin + etoposide (CE) with/without tiragolumab in patients with untreated extensive-stage SCLC (SKYSCRAPER-02), also reported that the addition of tiragolumab did not provide benefit [59]. A total of 490 patients were randomized (tiragolumab 600 mg IV + atezolizumab 1200 mg IV + CE, n=243; placebo + atezolizumab 1200 mg IV + CE, n=247). Median PFS was 5.1 months (tiragolumab + atezolizumab + CE) vs 5.4 months (placebo + atezolizumab + CE). Median OS was 13.1 in the tiragolumab + atezolizumab + CE arm compared to 12.9 months in the placebo + atezolizumab + CE arm. Grade 3/4 treatment related AEs occurred in 52.3% (tiragolumab + atezolizumab + CE) and 55.7% (placebo + atezolizumab + CE) and grade 5 treatment related AEs occurred in 0.4% (tiragolumab + atezolizumab + CE) and 2.0% (placebo + atezolizumab + CE) [59]. The combination was well tolerated, and no new safety signals were

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identified for the addition of tiragolumab to the treatment regimen. As of February 2022, the final OS analysis has not been completed. The clinical efficacy of adding tiragolumab to atezolizumab treatment is still being investigated, and as of June 2022, 5 additional phase 3 non-recruiting and recruiting trials testing the effects of this combination in several cancers (NSCLC, SCLC, esophageal [60], and cervical cancer) are active according to clinicaltrials.gov. Safety, pharmacokinetic, biomarker and immunogenicity analyses are scheduled in the upcoming SKYSCRAPER-07 trial [60]. Future studies could interrogate if high PD-L1 and TIGIT expression is required for clinical efficacy of this immune checkpoint combination, or if tumor histology influences the rate of response.

2.3 Rationale

Based on the efficacy of atezolizumab and tiragolumab in patients with solid tumors treated to date and in preclinical models of rare tumors, we propose a phase 2 trial in patients with rare, refractory solid tumors to evaluate the activity of this combination and explore predictive biomarkers of response and resistance. This study (RARE3) is the third of a series of connected phase 2 clinical trials evaluating drug combinations in patients with rare cancers; responses may trigger further evaluation of the treatment in that rare cancer type to evaluate response rate and mechanism-of-action.

2.4 Correlative Studies Background

This study affords a unique opportunity to collect information about the prevalence of mutations in genes associated with rare cancer, and about how patients' tumors respond to immunotherapy in the refractory tumor setting. Collecting tumor biopsy tissue on this trial will also make it possible to investigate the genomic and immune tumor microenvironment differences between responders and non-responders based on genomic/transcriptomic assays (including WES and RNA-seq),multiplex quantitative immunofluorescence assay panels, and evaluation of tertiary lymphoid structures (TLS). As the primary objective of this study is concerned with determining the proportion of activated tumor infiltrating CD8+ T cells following treatment in a rare cancer population, biopsies will be mandatory. We will additionally collect blood samples to look at cell-free DNA (cfDNA) to identify any mutations that may be associated with sensitivity or resistance to the drug combination. Collection of blood samples will be mandatory. In parallel, we will measure changes in the EMT and PD-L1 phenotype of CTCs and available tumor biopsies over time to explore any correlation with response to treatment or disease progression. The evaluation of the proportion of activated TILs will be integral, whereas all remaining biomarker studies on the protocol are considered exploratory; the data obtained will inform subsequent follow-up studies. The studies will be done in collaboration with NCI's Molecular Characterization Lab (MoCha) and the Pharmacodynamic Assay Development and Implementation Section (PADIS) at the Frederick National Laboratory for Cancer Research. The process for sample collection, shipping, and analysis is described in Section 5.3.

Tumor Biopsies (mandatory and optional)

Mandatory biopsies will be collected at baseline, and C3D1 (+/- 3 days); optional biopsies will be performed at time of progression or response. Biopsies will be assessed for the following:

- Tumor infiltrating CD8+ T cell density and activation status (mandatory) (PADIS).

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- Expression of PD-1/L1 in the tumor microenvironment (optional) (PADIS).
- Immune composition of the tumor microenvironment (optional) (PADIS).
- WES and RNASeq (optional) (MoCha).
- EMT markers (optional) (PADIS).
- Luminex assay for markers of cell death (optional) (PADIS).

Peripheral blood (mandatory)

Blood samples will be collected at baseline; every cycle on day 1; and at time of progression or response. Blood samples will be used for the following exploratory analyses:

- TSO 500 assay to examine genomic alterations in cell-free DNA (cfDNA) (MoCha).
- WES analysis to identify germline mutations (MoCha).
- EMT and PD-L1 analysis of CTCs (PADIS).

2.4.1 Tumor Biopsy Samples for Pharmacodynamic Assessment of Drug Response (mandatory)

Using the multiplex quantitative immunofluorescence assay (immunoPD IFA) platform developed by PADIS (**Figure 4**), we plan to quantify the number of activated CD8+ T cells infiltrating the tumor and characterize the activation status of the T cells around and within the tumor region. The tumor and T cell markers analyzed in the immunoPD IFA will include:

- PD-L1 expression
- T cell phenotypic marker CD8
- Phosphorylation of the T-cell receptor complex (TCR-CD3 ζ) to demonstrate antigen recognition by T cells [61]
- Tumor marker β-catenin, to identify tumor region

PADIS has demonstrated the use of this IFA in identifying and enumerating CD8+ T cells within tumor tissue that has been segmented using the tumor marker β-catenin. The number of activated CD8+ T cells present inside and outside of the tumor marker-positive area will be reported for biopsies collected at baseline and on Cycle 3 Day 1, as modulation of the tumor immune microenvironment is expected to require an extended response time frame. T-cell activation status will be determined through detection of pCD3ζ pY142phosphorylation. This

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endpoint will be correlated with patient response to immunotherapy. **Figure 4** shows the clinical feasibility of the immunoassay demonstrated in a tissue microarray core specimen.

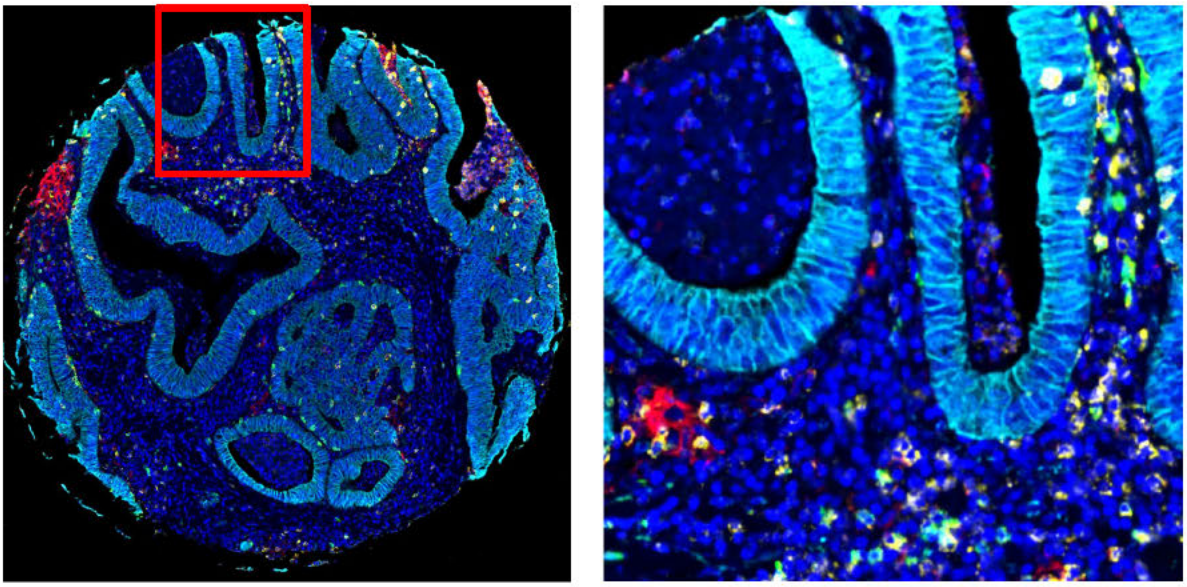

Figure 4: Performance of the immunoPD IFA on T cells captured in a colorectal cancer tumor microarray, demonstrating our ability to identify activated T cells in tissue specimens collected from patients under Developmental Therapeutics Clinic SOPs. Legend: CD8 (green/FITC channel); CD3ζpY142 (yellow/Cy3 channel); PD-L1 (red/Cy5 channel); β-Catenin (teal/Cy7 channel).

2.4.2 Tumor Biopsy Samples for Immunopharmacodynamic Assay Validation Summary (optional)

While there is evidence to suggest that PD-L1 expression is associated with response to anti-PD-1/PD-L1 checkpoint inhibitors, and to atezolizumab and tiragolumab combination [56] there are no data available to establish PD-L1 as a predictive biomarker for atezolizumab plus tiragolumab response in rare cancers. PADIS immunoPD IFA panels will be used to measure baseline expression of PD-1/L1 in responders and non-responders, as well as the effects of atezolizumab and tiragolumab on PD-L1 expression in tumor cells and PD-1 expression in T cells. Multiplex IFA panels measuring these markers in conjunction with CD3, CD8, and β-catenin are in development. Furthermore, an immunoPD IFA panel has been developed to measure expression of CD155 in the tumor microenvironment and of TIGIT on infiltrating T cells at baseline and following atezolizumab and tiragolumab treatment.

Finally, immune cell infiltration in the tumor micro-environment will be evaluated at baseline and following treatment to examine the effects of atezolizumab and tiragolumab on the antitumor immune response. For this purpose, we will employ multiplex IFA and IHC kits to follow changes in immune cell populations (CD8+ T cells, T-helper cells [CD4], T-regs [CD4, FOXP3], B cells [CD20, CD23], macrophages [CD68]) and tumor microenvironment (TIGIT, CD155) longitudinally and potentially correlate increases/decreases in specific immune populations with reduction in tumor burden. The data obtained from this continuous analysis may also inform the adjustment of biopsy timepoints to capture drug-induced immune changes in tumor tissue.

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2.4.3 Genetic Analysis (optional)

Tumor biopsy tissue will be used for exploratory whole-exome sequencing (WES) and RNA sequencing (RNA-Seq) as appropriate to identify tumor genomic alterations and gene expression patterns potentially associated with drug antitumor activity. RNA-Seq data will be compared to published immune signatures such as the Nanostring tumor inflammation signature (TIS) [62]. We will further explore how these signatures change after treatment (Cycle 3, Day 1) and at progression. Biopsy samples collected on another clinical trial within 3 months prior to registration where the patient has (a) had no intervening therapy and (b) the sample meets the requirements outlined in Section 5.3 may serve as baseline samples. Blood samples will also be collected for sequencing to enable comparison of tumor and germline sequences.

2.4.4 Markers of Apoptosis (optional)

Preclinical work exploring apoptosis/cell death biomarkers is ongoing in the lab of Dr. Apurva Srivastava, Frederick National Laboratory for Cancer Research. Tumor specimens will be evaluated for markers of apoptosis (e.g., cleaved caspase 3) and non-apoptotic cell death (e.g., necroptosis markers such as MLKL and formation of RIP1-MLKL and RIP3-MLKL heterodimers) using custom cell death Luminex assays developed by PADIS [63].

2.4.5 Epithelial-mesenchymal transition (EMT) (mandatory and optional)

Tumor and CTC samples collected on this study will undergo an assessment of epithelial-mesenchymal phenotype using a validated assay incorporating the epithelial marker E-cadherin and the mesenchymal marker vimentin. Treatment of carcinoma models with different anticancer drugs can cause changes in the tumor epithelial-mesenchymal character that potentially allows for rapid adaptation to therapy, creating a form of acquired drug resistance [64-66]. We are integrating EMT analysis into Developmental Therapeutics Clinic trials to monitor the emergence of drug resistance and for cells that may be responsible for tumor survival [66]. There are also data that the appearance of mesenchymal-like carcinoma cells in tumors causes the upregulation of cancer stem cell (CSC) markers which could signal an adverse prognosis, combining the poorer outcomes of increased tumor cell motility as well as "stemness." While the measurement of EMT markers in biopsies are optional on this study, we will collect mandatory blood samples for circulating tumor cells (CTCs) from patients over the course of their participation. Data from the single-agent study 14-C-0015 suggest that measuring EMT in CTCs may be an informative surrogate. We therefore hope that the examination of epithelial and mesenchymal markers in patient CTCs and any tumor biopsy samples will allow for the potential discovery of any associations between combination drug effect, patient response (including development of resistance to therapy), and EMT phenotype.

2.4.6 Blood samples for ctDNA (mandatory)

Blood for cell-free DNA (cfDNA) analysis will be collected before treatment, throughout the trial, and at the time of disease progression (optional). Once a patient has come off study, cfDNA from blood samples will be analyzed with the TSO500 ctDNA targeted sequencing assay or other platform to quantitatively assess longitudinal changes in cfDNA levels (e.g., levels, mutations, and fragmentation as a percentage of total circulating, cell-free DNA) and to support identification of any mutations that may be associated with sensitivity or resistance to the drug

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combination.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed rare solid tumors that have progressed on standard therapy or for whom there is no standard of care therapy. The list of eligible rare tumors can be found in Appendix C; other rare tumor types may be acceptable at the discretion of the PI.

- Patients must not be eligible for a higher priority study that would be feasible for them to enroll in, such as a disease specific study of phase 2 or higher or a randomized study. Specifically, patients who are eligible for the PEP-CTN pediatric trial of atezolizumab and tiragolumab in children, adolescents, and young adults with SMARCB1- or SMARCA4-deficient tumors should be excluded.

3.1.2 Patients must have measurable disease as defined by RECIST v1.1, with at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam). See Section 12 (Measurement of Effect) for details for the evaluation of measurable disease.

3.1.3 Patients must have a tumor site amenable to biopsy.

3.1.4 Age ≥18 years. Because biopsies are mandatory on this trial, patients <18 years of age are excluded.

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

3.1.6 Patients must have adequate organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– INR or aPTT*	≤1.5 institutional upper limit of normal (ULN)
– total bilirubin	≤ 1.5 x institutional ULN (however, patients with known Gilbert disease who have serum bilirubin level of up to 3 mg/dl may be enrolled)
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN (AST and/or ALT ≤5 × ULN for patients with liver involvement)
– creatinine	≤1.5 X institutional ULN OR
– creatinine clearance	levels ≥ 30 mL/min/1.73 m^2 are permitted as the study agents are not secreted by the kidney

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* Patients who receive therapeutic anticoagulation therapy should be on a stable dose.

3.1.7 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.8 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.9 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.10 Patients with **treated brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression for more than ≥1 month after treatment of the brain metastases.

3.1.11 Patients with **new or progressive brain metastases** (active brain metastases) or **leptomeningeal disease** are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.

3.1.12 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.13 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.14 Willingness to provide biopsy samples for research purposes.

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

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

3.2 Exclusion Criteria

3.2.1 Patients who have had prior monoclonal antibody therapy must have completed that therapy ≥5 weeks (or 3 half-lives of the antibody, whichever is shorter) prior to start of treatment (minimum of 1 week between prior therapy and study enrollment).

3.2.2 Patients must have recovered from clinically-significant adverse events of their most recent cancer immunotherapy to grade 1 or less, (with the exception of alopecia and

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lymphopenia).

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Prior anti-TIGIT therapy is not allowed. However, other prior immune checkpoint inhibitor therapy is permitted, provided it satisfies the conditions in section 3.2.1.

3.2.5 History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies (i.e., antibodies with generic names ending in "ximab" or "zumab", respectively) or fusion proteins, not resolved by pre-medication or steroids, leading to subsequent treatment cessation. Patients with a history of allergic reaction to chimeric or humanized antibodies for which symptoms never recurred after subsequent re-challenge may be considered after careful medical history review.

3.2.6 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone [>10 mg/day], cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

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

3.2.7 Patients with uncontrolled intercurrent illness, that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because atezolizumab and tiragolumab are investigational agents with unknown potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab, and because it is not known if tiragolumab can be excreted in human milk, breastfeeding should be discontinued if the mother is treated with atezolizumab.

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

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
- Patients with autoimmune hyperthyroid disease not requiring immunosuppressive treatment may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.

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

3.2.10 Patients with active tuberculosis (TB) are excluded.

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

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

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

3.2.14 Patients who have undergone major surgical procedures prior to Cycle 1, Day 1 who have not recovered to ECOG performance status ≤2 (Karnofsky ≥60%).

3.2.15 Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of 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 prior to Cycle 1, Day 1 or at any time during the study.

3.3 Inclusion of Women and Minorities

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

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childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

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

3.4 Screening Evaluation

Patient eligibility screening tests will be performed as described below. Eligibility history, physical examination, laboratory evaluations, and EKG are to be conducted within 8 days prior to enrollment on the research protocol. If protocol therapy is started within 8 days of these eligibility screening evaluations, values from the screening evaluations may be used as baseline measurements; if >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations and EKG must be repeated prior to starting protocol therapy. Baseline tumor imaging and ECHO must be performed within 28 days prior to start of protocol therapy. If protocol therapy is started within 28 days of the eligibility screening tumor imaging and ECHO, the screening evaluation imaging and ECHO results may be used as baseline measurements; if > 28 days have passed since the screening evaluation tumor imaging and ECHO, the imaging and ECHO must be repeated prior to starting protocol therapy.

3.4.1 Histologic confirmation: All patients are required to have histologically confirmed solid tumor(s). Pathology confirmation should preferably be done by the Laboratory of Pathology, NIH. However, pathology reports from outside institutions confirming the diagnosis of rare solid tumor will also be acceptable for eligibility purposes.

3.4.2 History and physical examination: Complete history and physical examination (including height, weight, vital signs, ECOG performance score, EKG) will be conducted within 8 days prior to both enrollment and the start of protocol therapy.

3.4.3 Imaging Studies (Baseline): Every participant should have an evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to both enrollment and the start of protocol therapy. In an occasional patient, MRI may be performed for a disease site instead of a CT scan if MRI is felt to provide more accurate measure of disease. MRI or CT scan with contrast of the brain, MRI liver, MRI for other disease sites, or bone scan may be done as clinically indicated.

3.4.4 Laboratory Evaluation: Baseline laboratory data are to be obtained within 8 days prior to both enrollment and the start of protocol therapy:

- Hematological Profile: CBC with differential.
- Biochemical Profile: ACTH, albumin, alkaline phosphatase, AM cortisol, amylase, total bilirubin, BUN, calcium, chloride, creatinine, LDH, lipase, phosphorus, total protein, SGOT[AST], SGPT[ALT], magnesium, potassium, and sodium, free T4, TSH.
- Urine analysis.
- Urine and/or serum pregnancy test for female participants of childbearing potential.

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3.4.5 Cardiac Evaluation

- EKG - to be performed within 8 days prior to enrollment and, if clinically indicated, also prior to start of protocol therapy
- ECHO - to be performed within 28 days prior to both enrollment and start of protocol therapy

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes 4 person registration types that are applicable to ETCTN trials.

- Investigator (IVR): MD, DO, or international equivalent,
- Non Physician Investigator (NPIVR): advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- Associate Plus (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, and
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A
CTEP-IAM Account with ID.me credentials	✓	✓	✓	✓
FDA Form 1572 • Practice sites, IRBs, and labs	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, certification, licensure, ABMS certification, GCP Training, personal	✓	✓	✓	

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Documentation Required	IVR	NPIVR	AP	A
statement, memberships, honors, publications, research support)				
GCP Training Certificated (mandatory file upload)	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional file upload)	✓	✓	✓	
Annual Re-registration	✓	✓	✓	✓

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster,
- Selection as the treating, credit, or consenting person in OPEN,
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

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

IRB Approval

Sites participating through the NCI Central Institutional Review Board (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 (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

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In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria to complete 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 record,
- Includes the IRB number of the IRB providing approval in the FDA Form 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the FDA Form 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),
- 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).

4.2.1 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 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 the screen
    - 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 *LAO-NCI*, and protocol number *10561*,
- 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.)

4.2.2 Protocol Specific Requirements For P10561 Site Registration

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Specimen Tracking System Training Requirement:

- All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
- Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
- The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time.This training will need to be completed before the first patient enrollment at a given site.

Please contact STS Support at Theradex for the training (STS.Support@theradex.com).

4.2.3 Submitting Regulatory Documents

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

To access the Regulatory Submission Portal, log on 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.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific 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 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.

4.2.4 Checking Site Registration Status

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

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol

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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 NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available 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 or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT system.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- 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, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Food and Drug Administration (FDA) Form 1572 in Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to 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. IWRS system also sends an email confirmation of the registration. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website.

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Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or 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 patient enrollment in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS 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.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link 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.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 8 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not

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receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, which can be found at the Clinical Research Operations website.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To[2]:
Archival (optional; additional to baseline biopsy)		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (optional)[1] If a block is not available, then submit: • Flash-frozen cores • 10-15 unstained, uncharged, air-dried slides (10 µm)	MoCha, FNLCR
Baseline (pre-treatment)		
	• 2 flash-frozen tumor cores (mandatory) • 1 flash-frozen tumor core (optional)[3] • 1 x 10 mL blood in Streck[4] tube (mandatory)	PADIS, FNLCR
	• 2 flash-frozen tumor cores (optional)[3] • 2 x 10 mL blood in Streck[5] tube (mandatory)	MoCha, FNLCR
Day 1 of Cycle 2 and each subsequent cycle (before drug administration)		
	• 2 x 10 mL blood in Streck[5] tube (mandatory)	MoCha, FNLCR
	• 1 x 10 mL blood in Streck[4] tube (mandatory)	PADIS, FNLCR
C3D1		
	• 2 flash-frozen tumor cores (mandatory) • 1 flash-frozen tumor core (optional)[3]	PADIS, FNLCR
	• 2 flash-frozen tumor cores (optional)[3]	MoCha, FNLCR
Progression/Response (optional)		
	• 3 flash-frozen tumor cores (optional)[3] • 1 x 10 mL blood in Streck[4] tube (mandatory)	PADIS, FNLCR
	• 2 flash-frozen tumor cores (optional)[3] • 2 x 10 mL blood in Streck[5] tube (mandatory)	MoCha, FNLCR

[1]If submitting slides, then slides must be processed in order, and numbered sequentially.
[2]See sections 5.3 and 5.5 for sample handling and shipping instructions.
[3]Remaining tumor cores will be distributed according to assay priority as shown in Table 3 in Section 5.6.
[4]RARECytetubes can be used if Streck tubes are not available.
[5]Streck tubes are mandatory for MoCha blood samples.

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5.2 Summary for Interventional Radiologist for Research Biopsies

All biopsy cores collected will be flash-frozen. Up to 5 core biopsies ≥18-gauge in diameter and ≥1 cm in length, or equivalent, will be obtained during each procedure. The required tumor content is >25%.

Mandatory biopsies will be collected at baseline and C3D1. Optional biopsies will be collected at time of disease progression/response.

For all biopsy time points, the core priority will be as follows:

- Cores 1 and 2:
    1) Tumor CD8+ cell infiltration (integral)
    2) Tumor CD8+ cell activation (integral)
    3) Tumor PD-1/L1 (exploratory)
    4) Immune cell infiltration (exploratory)
    5) EMT (exploratory)
- Cores 3 and 4:
    1) WES (exploratory)
    2) RNA-Seq (exploratory)
- Core 5:
    1) Markers of cell death (exploratory)

5.3 Specimen Collection and Processing

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

5.3.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted for WES and RNA-Seq analysis, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
    - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
    - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

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If an existing block cannot be submitted, the following are requested, if available:

- One (1) H&E slide (3-5 µm).
- A minimum of 10–15 x 10 µm unstained air-dried uncharged slides with tumor content >70%; submit 30–50 slides if tumor content is <70%.

Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with "1," and additional unstained slides should be processed next and be labeled 2 – n).

Labeling:

Include the following on all archival tissue specimens (i.e., FFPE block or slides):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (i.e., formalin-fixed paraffin-embedded [FFPE] Tissue)
- Tissue type (P for primary, M for metastatic or N for normal)
- Collection date (to be added by hand)
- Slide section number (to be added by hand)

5.3.2 Biopsy Collection

Serial tumor biopsies will be obtained by the biopsy team by a cutaneous approach, a dermatologist for skin lesions, or an ENT for lesions that are easily biopsiable through ENT exam. If possible, the lesion from which each biopsy is taken, and whether the specimen came from the center or periphery of the lesion, will be documented.

Acceptable biopsy procedures are:

- Percutaneous biopsy with local anesthetic.
- Excisional cutaneous biopsy with local anesthetic
- Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications < 2%
- Removal of additional tumor tissue during a medically necessary surgical procedure
- Biopsy with removal of additional tumor tissue during a medically necessary mediastinoscopy, laparoscopy, gastrointestinal endoscopy, bronchoscopy, or craniotomy

No open surgical, laparoscopic endoscopic procedure will be performed solely to obtain a biopsy for this protocol. If additional tissue is available from any patient and its collection poses no new risks to the patient, the tissue may be collected by NCI DCTD SOPs for use in any of the correlative studies described in Section 5 to which the patient has consented.

The use of imaging to facilitate biopsies will be decided by members of the biopsy team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to

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be of low risk to the participant, as determined by the investigators and the biopsy team. Cores from different areas of the tumor are preferred when feasible. The clinical, radiologic, dermatologic ENT and pharmacodynamic members of the research team will meet monthly to review the adequacy of the biopsy specimens for analysis.

Baseline biopsies will be performed following patient enrollment on study. If an initial attempt at percutaneous biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt at percutaneous biopsy. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed, but the patient will remain on study, receive study medication, and other correlative studies will be performed.

Five tissue cores per biopsy procedure will be collected if possible. Biopsy cores will be processed as described in NCI DCTD SOP340507 (http://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf).

Dermatologic and ENT biopsies should be collected per guidance from FNLCR PD Central Receiving (NCI_PD_Support@mail.nih.gov, 301-846-1951, or 301-846-6747).

Briefly, the biopsy cores (up to 5 per time point) or equivalent tissue, will be transferred into 1.5-mL pre-chilled cryovials and then flash frozen in liquid nitrogen. In accordance with SOP340507, biopsy specimens are collected into pre-chilled 1.5-mL Sarstedt, O-ring screw cap tubes and then flash-frozen in liquid nitrogen or a dry ice/ethanol bath, in accordance with SOP340507. It is ***imperative*** that biopsies are flash frozen *within 2 minutes of collection* in order to preserve key pharmacodynamic biomarkers. Biopsy samples will be analyzed as described above; any additional samples will be kept for future analysis in the Frederick National Laboratories CR Biorepository in liquid nitrogen freezers. Additional studies, if performed, will be conducted following an amendment to the current protocol. The batch record is included in SOP340507 and should be sent with every shipment along with the Rave STS shipping list report (see Section 5.4.2.2 for details).

Labeling:

Labels will be created through ETCTN STS, which include the following information:

- Patient ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (i.e. **Snap Frozen Tissue**)
- Tissue type (P for primary, M for metastatic or N for normal)
- Collection date (to be added by hand)
- Pass information (A, B, C, and D) (if a fifth core is collected, pass designator E should be added by hand on the no-pass designator label)

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5.3.3 Blood Collection

5.3.3.1 Blood collection for Genetic Analysis

Two whole blood samples will be collected at each of the following timepoints.

- on cycle 1 day 1 prior to treatment (baseline)
- on day 1 of each subsequent cycle (± 3 days for scheduling conflicts)
- at time of disease progression or response.

Baseline blood sample will be used for germline control analysis. Mononuclear cells from this blood sample will be isolated for nucleic acid extraction and exploratory WES to allow for germline and somatic variants to be accurately identified, and to enable the accurate assessment of mutational signatures in the tumor specimen.

Labeling:
Include the following on blood specimens:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type/Collection tube type (e.g.: blood/Streck)
- Collection date (to be added by hand)

Collect at least 7.5 mL of blood into each 10mL pre-labeled Streck tube and **gently** invert 8-10 times to mix. Blood must be thoroughly mixed to ensure preservation of specimen. Heparin should be avoided in pre-collection flush procedures. If therapeutic heparin dosing contamination is a possibility, then venipuncture is recommended as a first-choice collection method. If a Streck cfDNA tube immediately follows a heparin tube in the draw order, then collecting an EDTA tube as a waste tube prior to collection in the Streck Cell-Free DNA BCT is recommended.]

After collection, blood in Streck cfDNA tubes should never be refrigerated, as this will compromise the specimen. Blood collected in Streck cfDNA tubes is stable at room temperature.

Cell-free DNA (cfDNA) monitoring will be performed with the TSO 500 ctDNA assay or another platform and, potentially, WES to evaluate arising therapy-resistance mechanisms in the tumor. Patient plasma will be analyzed for ctDNA by the TSO 500 panel and, WES of cfDNA will also be considered to uncover additional relevant changes in the tumor genome; the results of these studies will not be returned to patients. Once a patient has come off study, cfDNA from blood samples correlating to clinically informative time points (minimally, before treatment and at restaging scans suggesting tumor growth) will be analyzed.

Residual cfDNA samples from this study may also be sent by MoCha for fragmentomic analysis performed by DELFI [67]. Results will be evaluated for correlation with tumor regression or progression.

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5.3.3.2 Blood Collection for CTC Studies

One whole blood sample (at least 7.5 mL in 10-mL Streck tubes) will be collected at each of the following time points**:**

- cycle 1 day 1 prior to treatment (baseline)
- day 1 of each subsequent cycle (± 3 days for scheduling conflicts)
- at time of disease progression/response

Tubes must be inverted 8 times to ensure adequate mixing of the additive that preserves the CTCs. Blood samples for CTC analysis **should be shipped within 24 hours of collection** so they can be analyzed within 48 hours of collection . CTC samples may not be collected on Fridays or any business day prior to a federal holiday or weekend.

Labeling:

Labels will be created through ETCTN STS, which include the following information:

- Patient study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type/Collection tube type (e.g., Blood/EDTA)
- Collection date (to be added by hand)

5.4 Specimen Tracking

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

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The tumor histology will be entered into Rave at enrollment.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

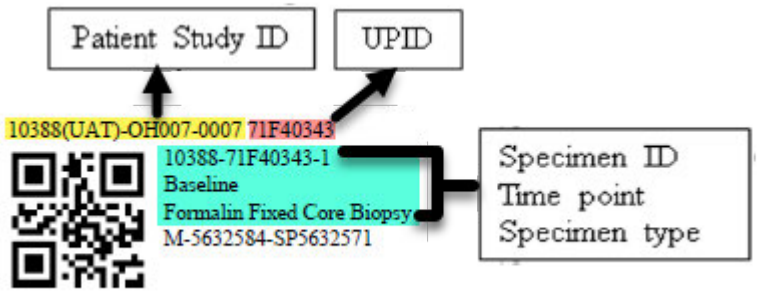
For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.4.1.1 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time.

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The last line on the example label is for the handwritten date and optional time.

5.4.2 Overview of Process at Treating Site

5.4.2.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.2.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and the collection time on each label. After collection, store labeled specimens as described in Section 5.3.
- Apply an extra specimen label to *each* report before scanning. Return to **Specimen Tracking Enrollment** CRF to upload the form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted**. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document** (either by adding a label or hand writing).

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Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print 2 copies of the shipping list, one to provide in the box, the other for your own records.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s). See sections 5.4.3–5.4.6 for details.

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Shipping of Specimens from Clinical Site to Other Laboratories

5.5.1 Archival Tissue Submission

Send notification to MoCha through Rave STS to advise that archival tissue is being prepared for shipment. If needed, contact MoCha directly at MoChaSampleReceiving@nih.gov.

Archival tumor tissue that is submitted (by all consenting patients) for genomic analysis exclusively may be either flash-frozen or formalin-fixed, paraffin-embedded (FFPE) and should be shipped via FedEx (using MoCha account number) to:

Attn: [redacted]
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room [redacted]
Frederick, MD 21702

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MoChaSampleReceiving@nih.gov

Please contact [redacted] at [redacted] (email: MoChaSampleReceiving@nih.gov) **to obtain the MoCha FedEx account number** or to ask any questions regarding storage or shipment of these specimens.

Send notification to MoCha through Rave STS to advise that archival tissue is being prepared for shipment. MoCha should be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s). Include a copy of the Shipping List report with all shipments.

5.5.2 Tumor Specimen Shipment

Biopsies will be collected, and flash frozen as above. Baseline biopsy specimens should be stored at -80°C or lower until the post dose (i.e. C3D1) biopsy is collected. For baseline biopsies for which the on-treatment matched biopsy could not be collected, please contact PADIS to arrange shipment.

First two cores at each collection timepoint (baseline; C3D1) , should be shipped on dry ice to PADIS as described below.

Sites are required to create a FedEx shipping label to accommodate the variable dry ice weight of the shipment package. Use only FedEx Priority Overnight Shipping. NCI-F PD Support will provide a FedEx account number to cover the cost of the shipment. By linking the NCI-F FedEx account number provided to the biopsy shipment, NCI-F PD Support can closely monitor the shipment and cover all shipping costs.

Shipping Address for Non-NIH Sites:

PD biopsies should be shipped per patient set via FedEx Priority Overnight (using the PADIS account number) to:

Attn: [redacted]
Natural Products and Tumor Repositories | Charles River
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21702
Phone: [redacted]

Please Note: Do not ship frozen biopsy specimens on Fridays or one day prior to any Federal holiday as FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. This prevents the risk of dry ice sublimation and loss of sample integrity.

Generate a shipping notification via Rave STS by checking the "email alert" box (see Section 5.4.2.2, Step 6). Prior to shipment of specimens, notify PADIS via NCI_PD_Support@mail.nih.gov if there are any protocol deviations or issues, which must be noted in the batch record included in SOP340507. One batch record must be completed per patient's biopsy specimens, per timepoint, with all required information noted. Ship a copy of

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the batch record(s) with the specimens, and retain a copy at the collection site. Also record any protocol deviations or issues in the Rave STS Specimen Transmittal form, in the comments section (which will be captured on the Rave STS Shipping List). Ship a printed copy of the Rave STS Shipping List with the specimens, as mentioned in Section 5.4.2.2, Step 5.

Please contact [redacted] (office: [redacted], cell: [redacted]) or [redacted] (office: [redacted] cell: [redacted]) (email: NCI_PD_Support@mail.nih.gov) to ask any questions regarding storage or shipment of these specimens.

Two additional cores should be shipped to the MoCha Laboratory at FNLCR for whole exome sequencing or RNA-Seq (baseline; C3D1; at response or progression).

Send notification to MoCha through Rave STS. MoCha should be notified of all protocol deviations or issues, prior to shipment of specimens(s). Include a copy of the Shipping List report with all shipments. **Do not ship frozen biopsy specimens on Fridays or one day prior to any Federal holiday** as FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. This prevents the risk of dry ice sublimation and loss of sample integrity.

Email the MoCha Histology group at MoChaSampleReceiving@nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the primary tumor, tracking information, and site information. MoCha should be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s).

Attn: [redacted]
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room [redacted]
Frederick, MD 21702

Please contact [redacted] at [redacted] (email: MoChaSampleReceiving@nih.gov) **to obtain the MoCha FedEx account number** or to ask any questions regarding storage or shipment of the restaging or progression biopsy specimens.

Any remaining core should be shipped to PADIS, as described above, for analysis of markers of cell death using the Luminex assay.

5.5.3 Blood for genetic analysis (cfDNA, WES at MoCha) shipment

Blood samples should be shipped at ambient temperature to the MoCha Laboratory at FNLCR via FedEx First Overnight or FedEx Priority Overnight. The MoCha Lab will provide a FedEx account number to cover the cost of the shipment.

Please contact [redacted] at [redacted] (email: MoChaSampleReceiving@nih.gov) **to**

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obtain the MoCha FedEx account number or to ask any questions regarding storage or shipment of these specimens.

Send notification to MoCha through Rave STS. MoCha should be notified of all protocol deviations or issues, prior to shipment of specimens(s). Include a copy of the Shipping List report with all shipments.

Samples should **arrive at MoCha within 2 days of collection when possible; arrival within 3 days of collection is permissible when necessary**. Note that FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. **Therefore, these blood samples should not be collected on a Friday, or the day before a Federal holiday.**

Ship blood specimens at ambient temperature via FedEx (using MoCha account number) to:

Attn: [redacted]
MoCha Histology Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 321 Room [redacted]
Frederick, MD 21702

5.5.4 Blood for CTC analysis (PADIS) shipment

Samples should be shipped by FedEx Priority Overnight Shipping using a FedEx account number provided by NCI-F PD Support.

Prior to CTC collection, each participating site should e-mail NCI_PD_Support@mail.nih.gov with a request for specimen collection and shipping materials. Allow at least six business days for receipt of the blood shipment containers; a confirmation e-mail with the expected shipping date will be sent.

Please contact [redacted] (office: [redacted], cell: [redacted]) or [redacted] (office: [redacted], cell: [redacted]) (email: NCI_PD_Support@mail.nih.gov) **to obtain the PADIS FedEx account number** or to ask any questions regarding storage or shipment of these specimens.

Upon receiving email notification of the shipment from RAVE specimen tracking, FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) will send a confirmation e-mail that personnel will be available on the expected delivery date and time. Personnel are generally available to receive CTC sample shipments Tuesday through Friday, exclusive of government holidays. All shipments should include a description of contents on the outside label/shipping slip, and a detailed packing slip should be included with the samples. Because of the 48-hour window of CTC sample stability, CTC samples should be shipped to arrive when specified below:

Collection Day	Day/time samples **must** arrive at PADIS
Monday	Wednesday (early morning)
Tuesday	Thursday (early morning)

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Wednesday	Friday (early morning)
Thursday	Friday (early morning)
Saturday	Monday (early morning)
Sunday	Tuesday (early morning)

CTC samples may not be collected on Fridays and/or any business day prior to a Federal Holiday, due to shipment and processing requirements. Scheduled CTC collections that fall on a Friday are waived.

Shipping Address for Non-NIH Sites:

Blood specimens should be shipped on the day of collection via FedEx (using PADIS account number) to:

Attn: [redacted]
NCI-F/FNLCR
Natural Products and Tumor Repositories | Charles River
1073 Beasley Street, Building 1073
Fort Detrick
Frederick, MD 21702
Phone: [redacted]

5.6 Biomarker Plan

To assess the effect of atezolizumab and tiragolumab on the antitumor immune response, the proportion of activated CD8+ T cells in tumor samples will be evaluated at baseline and after treatment (cycle 3 day 1) using multiplex immunofluorescence assays.

Integral protocol markers:

1. CD8/ β-catenin IFA
2. CD8, CD3, CD3ζ-pY142 IFA

Contextual markers that will be used to interpret integral study markers:

1. PD-1/L1 IFA—exploratory
2. Immune cell infiltration in the tumor micro-environment (CD4, FOXP3, CD8, CD20, CD68, CD11, TIGIT, CD155)—exploratory
3. Tumor mutational burden—exploratory
4. EMT (phenotypic markers of epithelial and mesenchymal states such as E-cadherin, vimentin, and β-catenin)—exploratory
5. Apoptosis: γH2AX/Cleaved Caspase 3—exploratory

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List of Biomarker Assays in Order of Priority

Note for participating sites: Please see Section 5.1 for details on specimens to collect.

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	CD8+ T-cell infiltration into tumor	PADIS I/O PD Multiplex IFA (CD8 and β-catenin) CLIA: N	Integral To examine the effects of atezolizumab and tiragolumab on the antitumor immune response	Tumor biopsy tissue	Baseline,C3D1. Progression/ response*	M & O*	PADIS, FNLCR [redacted]
2	CD8+ T cell activation markers	PADIS I/O PD Multiplex IFA (CD8, CD3, CD3ζ-pY142) CLIA: N	Integral To examine the effects of atezolizumab and tiragolumab on tumor-infiltrating T cell activation	Tumor biopsy tissue	Baseline, C3D1. Progression/ response*	M & O*	PADIS, FNLCR [redacted]
3	PD-1/ PD-L1 Tumor expression	PADIS I/O PD Multiplex IFA (PD-1, PD-L1, β-catenin) CLIA: N	Exploratory To examine the effects of atezolizumab and tiragolumab on the antitumor immune response	Tumor biopsy tissue	Baseline, C3D1, progression/ response	O	PADIS, FNLCR [redacted]

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Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
4	Immune cell infiltration in the tumor micro-environment	PADIS I/O PD Multiplex IFA and IHC kits (CD4, FOXP3, CD8, CD20, CD68, CD11, TIGIT, CD155) CLIA: N	Exploratory To examine the effects of atezolizumab and tiragolumab on the antitumor immune response	Tumor biopsy tissue	Baseline, C3D1, progression/ response	O	PADIS, FNLCR [redacted]
5	Tumor mutational burden/ gene variants	Whole-exome sequencing (WES) and RNASeq CLIA: N	Exploratory To uncover mutations in key pathways (immune response, antigen presentation) that may be correlated with patient response to atezolizumab and tiragolumab	Tumor biopsy tissue	Baseline**, C3D1, progression/ response	O	MoCha Laboratory, FNLCR [redacted]
6	EMT	EMT Panel IFA CLIA: N	Exploratory To explore tumor adaptation to drugs over time	Tumor biopsy tissue	Baseline, C3D1, progression/ response	O	PADIS, FNLCR [redacted]

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Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
7	Markers of cell death, including apoptosis	Luminex assay CLIA: N	Exploratory To explore drug combination mechanism of action	Tumor biopsy tissue	Baseline, C3D1, progression/ response	O	PADIS (FNLCR) National Clinical Target Validation Laboratory (NCTVL) [redacted]
* Biopsy collection at time of progression/response is optional. **Archival FFPE tissue can be used for baseline analysis if available and if archival sample was collected within the preceding six months							
Blood-based Biomarkers							
1	Germline DNA control for WES†	WES CLIA: N	Exploratory To compare germline genomic profile to tumor specimen	PBMC	Baseline	M	MoCha Laboratory, FNLCR [redacted]
2	Gene variants found in cell-free, cell-free DNA†‡	TSO 500 ctDNA CLIA: N	Exploratory Hypothesis generation: to evaluate DNA alterations found in cell-free DNA and their potential correlation with response to the combination	Peripheral blood plasma	Baseline; first day of each subsequent cycle; progression/ response	M	MoCha Laboratory, FNLCR [redacted]
3	EMT PD-L1	EMT Panel IFA PD-L1 IFA CLIA: N	Exploratory To explore tumor adaptation to drugs over time	Peripheral blood CTCs	Baseline; first day of each subsequent cycle; progression/ response	M	PADIS, FNLCR [redacted]

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Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
† Germline DNA for WES at baseline will be performed on the same vial collected for cfDNA analysis. PBMCs will be isolated for WES, and cfDNA will be analyzed from the plasma. ‡ Residual cfDNA samples from this study may also be sent for fragmentomic analysis performed by DELFI.							

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6. TREATMENT PLAN

This is an open-label, single-arm, phase 2 trial evaluating the combination of atezolizumab with tiragolumab in adult subjects ≥18 years of age with rare, refractory solid tumors.

Doses and drug administration are defined in Section 7.

Treatment plan: Each treatment cycle is 21 days long (cycle can start up to 8 days late due to scheduling conflicts; day 1 is the first day treatment is administered). Atezolizumab and tiragolumab will be administered IV on day 1 of each cycle.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, laboratory evaluations, and EKG are to be conducted within 8 days prior to the start of protocol therapy. If protocol therapy is started within 8 days of these eligibility screening evaluations (see Section 3.4), values from the screening evaluations may be used as baseline measurements; if >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and EKG must be repeated prior to starting protocol therapy. Baseline tumor imaging scans and ECHO must be performed within 28 days prior to start of protocol therapy. If protocol therapy is started within 28 days of the eligibility screening tumor imaging, the screening evaluation imaging results may be used as baseline measurements; if > 28 days have passed since the screening evaluation tumor imaging, the imaging must be repeated prior to starting protocol therapy.

CT scans will be performed at baseline (within 28 days prior to start of protocol therapy), at the end of cycle 3, and repeat scans will be performed every 2 cycles (every 3 cycles for patients on study more than 1 year and every 4 cycles for patients on study more than 3 years). Response assessment will be performed using RECIST 1.1. Response will also be explored using iRECIST (see Section 12.2). Following treatment with immune checkpoint inhibitors complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden, characterized by progressive disease by traditional response criteria. Documentation must be provided for patients removed from study for progressive disease.

History and physical examination will be done within 8 days of Day 1 of cycle 1, and within 3 days of all subsequent cycles. Labs (CBC with differential; serum chemistries) will be performed at baseline as described above, on every treatment week before drug administration (laboratory evaluation may be performed up to 3 days prior to scheduled date to accommodate scheduling conflicts and patient convenience). EKG will be obtained at baseline and as clinically indicated thereafter.

All toxicities will be reported for all patients who receive any amount of study drug on this study. Evaluation of toxicity will begin with study drug administration on cycle 1 day 1.

Mandatory tumor biopsies will be collected at baseline and on cycle 3 day 1 (1 ± 1 day). In addition, an optional biopsy may be performed at response or disease progression.

Blood samples for PD and genomic studies are mandatory for all patients, and will be collected at baseline (for germline genomic analysis) and on day 1 of every subsequent cycle before drug

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administration (for CTC and cfDNA analysis); and at time of response/disease progression follow-up biopsy.

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Administration of atezolizumab and tiragolumab will be performed in a setting with emergency management capabilities and staff who are trained to monitor for and respond to medical emergencies.

Doses are fixed and not dependent on body weight. There will be no dose reductions in this study. Appropriate dose delays are described in Section 7. 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				
Agent	***Dose***	***Route***	***Schedule***	***Cycle Length***
Tiragolumab	600 mg	IV	Day 1 of each cycle	21 days
Atezolizumab	1200mg	IV	Day 1 of each cycle	21 days

6.1.1 Atezolizumab Administration and Monitoring Instructions

6.1.1.1 Atezolizumab Dose Preparation

The prescribed dose of atezolizumab should be diluted in 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused through a 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP); the IV infusion line may be constructed of PVC, PE, or polybutadiene (PB); and the 0.2 or 0.22 micrometer in-line filter may be constructed of polyethersulfone (PES) or polysulfone (PSU). The prepared solution may be stored at 2°C–8°C for up to 24 hours or at ambient < 25°C (77°F) for 8 hours. If the dose solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. This time includes storage and time for administration for infusion. Do not shake or freeze infusion bags containing the dose solution.

6.1.1.2 Atezolizumab Administration

Atezolizumab is administered prior to tiragolumab as an intravenous infusion over 60 (+/- 10) minutes and infused through a line with a 0.2 µm or 0.22 µm PES or PSU in-line filter. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 (+/- 10) minutes. The first infusion of atezolizumab will be followed by a 30-minute observation period. For subsequent cycles, if no infusion related reactions are recorded, the observation period can be removed. Do not administer atezolizumab as an intravenous push or bolus.

Atezolizumab should be administered over 60 (+/- 15) minutes, followed by a 60 minutes observation period, if the patient experiences an infusion related reaction (IRR) during the previous infusion of atezolizumab.

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Administration of First and Subsequent Atezolizumab Infusions

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.

6.1.2 Tiragolumab Administration and Monitoring Instructions

6.1.2.1 Tiragolumab Administration

Tiragolumab will be administered after atezolizumab and will be infused over 60 (+/- 10) minutes and infused through a 0.2 or 0.22 µm polyethersulfone (PES) or polysulfone (PSU) filter (see details in subsequent table). On Cycle 1 Day 1 tiragolumab will be administered 30 (±10) minutes after atezolizumab. If no atezolizumab-infusion-related reactions occur, the drugs can be administered sequentially in subsequent cycles.

If the first infusion is tolerated, all subsequent infusions may be delivered over 30 (+/- 10) minutes. The first infusion of tiragolumab will be followed by a 30-minute observation period. For subsequent cycles, if no infusion related reactions are recorded, the observation period can be removed.

No premedication is permitted for administration of Cycle 1 of atezolizumab or tiragolumab.

Patients who experience an infusion related reaction (IRR) with previous cycles of tiragolumab or atezolizumab may receive premedication with antihistamines and/or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions (see Section 6.2).

Tiragolumab should be administered over 90 (+/- 10) minutes, followed by a 60 minutes observation period, if the patient experiences an IRR during the previous infusion of

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tiragolumab.

Administration of First and Subsequent Tiragolumab Infusions

Study Drug	First Infusion	Subsequent Infusions
Infusion of tiragolumab	• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) are recommended to be monitored within 60 minutes prior to the infusion, if feasible. • Tiragolumab should be infused over 60 (+/-10) minutes. • Vital signs are recommended to be monitored every 15 (+/-5) minutes during the infusion and at 30 (± 10) minutes after the infusion.	• 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 monitored during the infusion if clinically indicated. • Tiragolumab 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.

6.1.3 Anaphylaxis Precautions and Procedures

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, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

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

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1. Stop the study drug infusion.
2. Call for additional medical assistance.
3. Ensure that appropriate monitoring is in place, with continuous EKG and pulse oximetry monitoring, if possible.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.
6. Draw serum/plasma samples for immunogenicity testing.
7. Ask participant to return for washout immunogenicity sample if appropriate.

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of atezolizumab and/or tiragolumab 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 Principal Investigator 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. Appendix B (Patient Drug Information Handout and Wallet Card) is available.

Palliative radiotherapy to non-targeted lesions may be permitted for patients receiving atezolizumab and tiragolumab after completing 2 cycles of therapy and achieving stable or responding disease, at the Principal Investigator's discretion.

Drugs to be avoided:

- Traditional herbal or homeopathic or natural medicines should be limited and used at the discretion of the investigator
- Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.
- Immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, anti-TNF-α, or IL-2 (aldesleukin) (prohibited prior to and during the study and for 10 weeks after the last dose of atezolizumab; see Section 3.2.6). These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab.
- Live vaccines and live, attenuated vaccines (prohibited during the study and for 100 days after the last dose of study drug).
- Initiation of granulocyte colony-stimulating factors (e.g., filgrastim and biosimilar products, sargramostim, and/or pegfilgrastim) should be discussed with the Medical Monitor.

Patients are permitted to use the following therapies during the study:

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- Oral contraceptives with a failure rate of < 1% per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated influenza vaccinations
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for COPD or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

6.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
    - With the caveat that patients who show evidence of clinical benefit may be permitted to continue atezolizumab and tiragolumab treatment after disease progression, if they meet the criteria outlined in Section 12.2.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(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 non-compliance
- Pregnancy
    - All women of childbearing 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.
    - Patient may resume therapy after completion of pregnancy, at the discretion of the investigator and if the patient had been deriving benefit from the therapy.
- Termination of the study by sponsor
- 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 Case Report Form (CRF).

6.4 Duration of Follow-Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed

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related to the therapy. Toxicities felt to be possibly, probably, or definitely related to the study drugs that have not resolved or stabilized by Day 30 post-treatment will be followed until stabilization or resolution via phone calls as clinically indicated.

6.5 Criteria for Removal from Treatment and/or Study

Patients will be removed from study for one of the following reasons: completed 30-day follow-up period or toxicities are unresolved but stabilized, patient enrolls on another protocol, patient receives other type of treatment-intent therapy, pregnancy, or death. The reason for study removal and the date the patient was removed must be recorded on the case report form.

7. DOSING DELAYS/DOSE MODIFICATIONS

There will be no dose reduction for atezolizumab and tiragolumab 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 and/or tiragolumab are held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from treatment 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 and tiragolumab 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.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab and tiragolumab; for higher-grade irAEs, atezolizumab and tiragolumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab and tiragolumab or the use of steroids. Assessment of the benefit risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab and tiragolumab should be permanently discontinued in patients with life threatening irAEs.

7.1 Agent Specific Dose Toxicity Management

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7.1.1 Infusion-Related Reactions

No premedication is permitted for the administration of Cycle 1 of atezolizumab or tiragolumab. However, patients who experience an infusion-related reaction (IRR) with atezolizumab or tiragolumab may receive premedication with antihistamines and anti-pyretic medications for subsequent infusions.

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

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

Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue atezolizumab or tiragolumab and contact study chair.

IRR = infusion-related reaction.

7.1.2 Cytokine-Release Syndrome (CRS)

No premedication is permitted for the administration of Cycle 1 of atezolizumab or tiragolumab.

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However, patients who experience CRS with atezolizumab or tiragolumab may receive premedication with antihistamines and antipyretics for subsequent infusions.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction [68]. CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 including atezolizumab.

Severe COVID-19 is associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ [69]. If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Management Guidelines for Cytokine-Release Syndrome

Event	Management
Grade 1 [a] fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance IV fluids • 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, antipyretics, and/or analgesics, and monitor closely for CRS.
Grade 2 [a] fever [b] with at least one of the following: Hypotension not requiring vasopressors Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix.

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Event	Management
	• Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 5 mg/m^2/day (maximum 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 or tiragolumab, and contact study chair. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab or tiragolumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact study chair.

Event	Management
Grade 3 [a] Fever [b] with at least one of the following: • Hypotension requiring a vasopressor (with or without vasopressin) • Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab or tiragolumab and contact study chair. • 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 5 mg/m^2/day (maximum 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.
Grade 4 [a] Fever[b] with at least one of the following: • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring	• Permanently discontinue atezolizumab or tiragolumab and contact study chair. • Administer symptomatic treatment. • 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.,

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Event	Management
oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	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 5 mg/m^2/day (maximum10 mg) every 6 hours. • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments f may be considered at the discretion of the investigator and in consultation with the study chair. • 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; MAS = macrophage activation syndrome;
NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.
The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on the ASTCT CRS Consensus Grading Scale. NCI CTCAE v5.0 and the ASTCT CRS Consensus Grading Scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome 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.

7.1.3 Pulmonary Events

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

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab.

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.

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Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and tiragolumab 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 and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab. [a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study chair. • 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 and tiragolumab and contact study PI. • Bronchoscopy or BAL is recommended. • 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.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 5 mg/m^2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.4 Hepatic Events

Immune-mediated hepatic events are a potential risk with tiragolumab. Immune-mediated hepatitis has been associated with the administration of atezolizumab.

Eligible patients must have adequate liver function, as manifested by measurements of bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.

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

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

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Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab and tiragolumab. • 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 and tiragolumab for up to 12 weeks after event onset. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab. [a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact study PI. • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 5 mg/m^2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.5 Gastrointestinal Events

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

Immune-mediated colitis has been associated with the administration of atezolizumab.

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

Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

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Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab and tiragolumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab. [a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Diarrhea or colitis, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab • 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] If corticosteroids have been initiated, they must be tapered over ⩾ 1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.6 Endocrine Events

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

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been

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associated with the administration of atezolizumab.

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

Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab and tiragolumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Symptomatic hypothyroidism	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab and tiragolumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab and tiragolumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider referring to endocrinologist.
Symptomatic hyperthyroidism	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab and tiragolumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and tiragolumab and contact study chair for life threatening immune-mediated hyperthyroidism.
Symptomatic adrenal insufficiency, Grade 2–4	• Hold atezolizumab and tiragolumab for up to 12 weeks after event onset. • Refer patient to endocrinologist.

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Event	Management
	• 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study chair.

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

[a] If corticosteroids have been initiated, they must be tapered over ⩾ 1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

Event	Management
Hyperglycemia, Grade 2	• Continue atezolizumab and tiragolumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset • Initiate treatment with insulin. • Monitor for glucose control. • 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 and tiragolumab when symptoms resolve and glucose levels are stable.
Hypophysitis (panhypopituitarism), Grade 2 or 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • 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.

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Event	Management
	• If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (panhypopituitarism), Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact study PI. • 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.

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

[a] If corticosteroids have been initiated, they must be tapered over ⩾ 1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.7 Ocular Events

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

Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab and tiragolumab. • 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 and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact study PI.

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Event	Management
	• 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] If corticosteroids have been initiated, they must be tapered over ⩾ 1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.8 Immune-mediated Cardiac Events

Immune-mediated myocarditis and pericarditis have been associated with the administration of atezolizumab. Management guidelines for cardiac events are provided in the table below.

7.1.8.1 Immune-Mediated Myocarditis

Immune-mediated myocarditis is a potential risk with tiragolumab and 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 or associated with pericarditis (see section on pericardial disorders below) 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 table below.

7.1.8.2 Immune-Mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related

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(post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

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

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Event	Management
Immune-mediated myocarditis, Grade 2–4 Immune-mediated pericardial disorders, Grade 2–4	• Permanently discontinue atezolizumab and tiragolumab, contact study PI. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis 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.

7.1.9 Pancreatic Events

Immune-related pancreatic events are a potential risk with tiragolumab. Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab and tiragolumab. • Monitor amylase and lipase weekly.

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Event	Management
	• 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 and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study chair. • For recurrent events, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study chair. • For recurrent events, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact study PI. • 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.

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[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.10 Dermatologic Events

Immune-related dermatologic events are a potential risk with tiragolumab. Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-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

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab and tiragolumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab and tiragolumab. • Consider patient referral to dermatologist. • 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 and tiragolumab for up to 12 weeks after event onset. • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 5 mg/m^2/day (max 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact study chair.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab and tiragolumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.

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	• Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab and tiragolumab.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.11 Neurologic Disorders

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

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

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

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

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact study chair. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

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Event	Management
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and tiragolumab and contact study chair[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).

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

7.1.12 Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is a potential risk with tiragolumab.

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated 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.

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

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

Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and tiragolumab and contact study chair. • 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.

7.1.13 Renal Events

Immune-mediated nephritis is a potential risk with tiragolumab and 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 nonsteroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab and tiragolumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.

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Event	Management
Renal event, Grade 2	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and tiragolumab and contact study PI. • 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] If corticosteroids have been initiated, they must be tapered over ⩾ 1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.14 Immune-Mediated Myositis

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

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

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

Management Guidelines for Immune-Mediated Myositis

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

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Event	Management
Immune-mediated myositis, Grade 2	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset and contact study PI. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study PI.
Immune-mediated myositis, Grade 3	• Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset and contact study PI. • 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 and tiragolumab.[a] • If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact study chair. • For recurrent events, treat as a Grade 4 event.

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Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and tiragolumab and contact study PI. • 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.

[a] If corticosteroids have been initiated, they must be tapered over ⩾1 month to the equivalent of ⩽ 5 mg/m2/day (max 10 mg/day) oral prednisone before atezolizumab and tiragolumab can be resumed.

7.1.15 Hemophagocytic lymphohistiocytosis and Macrophage Activation Syndrome
Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following 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 < 100×10^9/L (100,000/μL)
ANC < 1.0×10^9/L (1000/μL)
Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
Hemophagocytosis in bone marrow, spleen, lymph node, or liver
Low or absent natural killer cell activity
Ferritin > 500 mg/L (500 ng/mL)
Soluble 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[70]. A febrile patient should be classified as having MAS if the

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following criteria are met:

Ferritin > 684 mg/L (684 ng/mL)
At least two of the following:
Platelet count ≤ 181 × 10^9/L (181,000/μL)
AST ≥ 48 U/L
Triglycerides > 1.761 mmol/L (156 mg/dL)
Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 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 two heavy chains

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(448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells [18].

How Supplied:

Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Atezolizumab is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, at a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

Preparation:

The prescribed dose of atezolizumab should be diluted in 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused through a 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP); the IV infusion line may be constructed of PVC, PE or polybutadiene (PB); and the 0.2 or 0.22 micrometer in-line filter may be constructed of polyethersulfone (PES) or polysulfone (PSU). The prepared solution may be stored at 2°C-8°C for up to 24 hours or at ambient $\leq$ 25°C (77°F) for 8 hours. If the dose solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. This time includes storage and time for administration for 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 intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated

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for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions.

Potential Drug Interactions:

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

Patient Care Implications:

Female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 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 13.5).

8.2 Tiragolumab (NSC 827799)

Other Names: RO7092284, MTIG7192A

Classification: fully human (IgG1/kappa mAb) monoclonal antibody

Mode of Action:

Monoclonal antibody that binds to TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains), mediator of antibody-dependent cellular cytotoxicity (ADCC). Tiragolumab targets TIGIT on activated T-cell and natural killer (NK) cell subsets and prevents interaction with CD155 (poliovirus receptor [PVR]).

Description:

Tiragolumab is a fully human immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells.

How Supplied:

Roche/Genentech supplies and DCTD, CTEP, PMB distributes a single-dose vial that is preservative-free, sterile and contains a colorless to slightly yellow liquid containing 600 mg / 10 mL (60 mg/mL) of tiragolumab drug product buffered in a histidine solution containing polysorbate 20, sucrose, L-methionine, and WFI.

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Preparation:

Tiragolumab should be prepared in a 100 or 250 mL IV infusion bags containing normal saline (0.9% NaCl) and constructed with product contacting materials of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), and/or polypropylene (PP). The final concentration of tiragolumab in the infusion bag should be between 0.2 mg and 12 mg/mL.

Compatibility:

Due to the high level of siliconization, the use of **Venflon• Pro Safety** catheters from BD may lead to the formation of proteinaceous visible and subvisible particles. **Therefore, these catheters should not be used.**

Compatibility with Closed System Transfer Devices or Needle Free Transfer Devices Based on a review and assessment of exposure scenarios in a typical healthcare setting (i.e., during preparation and administration by IV infusions or subcutaneous or intravitreal administrations), healthcare worker exposure to tiragolumab is expected to be negligible. As a result, Closed System Transfer Devices (CSTDs) are not required from an occupational health risk perspective as a supplemental control in addition to the containment primary engineering controls (C-PECs) (e.g. ventilated devices) and containment secondary engineering controls (C-SECs) (e.g. rooms meeting specific criteria) specified in USP General Chapter 800 Hazardous Drugs-Handling in Healthcare Settings. Compatibility between tiragolumab and closed system transfer devices (CSTDs) or needle free transfer devices has not been assessed. If CSTDs or needle free transfer devices must be used to comply with site regulations, the site should be aware that their use may lead to the introduction of particles and may not allow the withdrawal of the labeled quantity of drug from the vial. Sites should perform a thorough visual inspection of the IV bag for particulates and dispose of any that contains particulates.

Storage:

Store tiragolumab between 2°C–8°C (36°F to 46°F) and protected from light. Do not freeze or shake.

If a storage temperature excursion is identified, promptly return tiragolumab to 2°C to 8°C (36°F to 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:

The prepared infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, the prepared infusion may be stored refrigerated at 2–8°C (36–46°F) for up to 24 hours prior to administration. Within this 24-hour storage period, the prepared infusion may be temporarily held at room temperature up to a maximum of 4 hours. The infusion time is separate from the 4 hour allowed time at room temperature. The prepared infusion should be discarded if the cumulative storage time prior to administration exceeds 24 hours.

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Route of Administration: intravenous (IV)

Method of Administration*:*

Tiragolumab should be infused through a dedicated infusion line. If a dedicated infusion line/catheter is not feasible, infusion lines and catheters must be flushed before and after administration of tiragolumab to ensure that tiragolumab does not contact other drug solutions.

Prepared tiragolumab infusions should be infused through an infusion line equipped with a 0.2 or 0.22 µm polyethersulfone (PES) or polysulfone (PSU) filter and infused over 20 to 75 minutes.

Potential Drug Interactions*:*

No specific pharmacokinetic (PK) or pharmacodynamic (PD) drug interaction studies have been conducted.

Patient Care Implications:

Women of childbearing potential and male partners of such women should take necessary precautions to avoid pregnancy while on tiragolumab and continue contraceptive measures for 90 days after the last dose.

Infusion Related reaction (IRRs associated with hypersensitivity reactions, target-mediated cytokine release, and/or emergent ADAs may occur. Infusion reactions may be mild in nature or may be severe.

Availability

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

If the study agent is provided by the NCI under a Collaborative Agreement with the agent manufacturer, the text below must be included in the protocol. Information on the study agent's Collaborative Agreement status will be provided in the approved LOI response letter.

Tiragolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.3 Agent Ordering and Agent Accountability

8.3.1.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-

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supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order atezolizumab and tiragolumab once a patient has been registered to the study.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. 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.

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

8.3.3 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, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.3.4 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://ctepcore.nci.nih.gov/OAOP
- 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)

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9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This drug screening study has one primary objective: to evaluate whether patients with advanced rare cancers have biologically significant changes in the proportion of active CD8+ T cells infiltrating the tumor after treatment with atezolizumab and tiragolumab (at the beginning of cycle 3 of treatment with the combination, compared to baseline). The secondary objectives are to measure objective tumor response rate (ORR), PD response rate (the proportion of patients with a clinically promising increase in CD8+ T cell infiltration, defined as more than 1.5 SD [as measured at baseline]), and PFS time. Other endpoints are exploratory.

The primary endpoint of this trial is detection of an increase in the proportion of active CD8+ T cells infiltrating the tumor after treatment with atezolizumab and tiragolumab, at the beginning of cycle 3 compared to baseline. Fifteen enrolled patients will yield 10 patients with evaluable paired biopsies with .95 probability, yielding 88% power, at the 1-sided .05 significance level, to detect an increase more than 1.25 SD (as measured at baseline), and to declare the combination promising with respect to the primary PD endpoint. This number will also be sufficient for assessment of the secondary endpoint of ORR; there will be 96.5% likelihood of seeing at least 1 objective tumor response assuming a true ORR of 20%. (Patients who do not achieve at least an unconfirmed response within 9 months [must be subsequently confirmed] will be considered non-responders for purposes of this analysis.)

There are no planned interim analyses for the aggregate study population; however, if none of the first 3 patients within a given histologic subtype achieve a confirmed response, that subtype will be closed to further accrual. For the purpose of efficacy evaluation in sarcoma or not otherwise categorized (NOC) tumors, the three patients must have the same histologic subtype. Per RECIST v 1.1 guidelines, the analysis will include all eligible patients who have initiated treatment.

9.2 Sample Size/Accrual Rate

To allow for approximately 15% ineligibility, a maximum of 15 patients will be enrolled across all eligible rare histologies to obtain 10 evaluable patients. It is anticipated that 1 patient per month may be enrolled onto this study, and that 12-15 months will be required to accrue the number of patients necessary to complete the trial.

PLANNED ENROLLMENT REPORT

PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2

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PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	3	3	1	1	8
More Than One Race	1	0	0	0	1
Total	7	6	1	1	15

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9.3 Analysis of Exploratory Endpoints

It is anticipated that non-parametric analyses will be used for these evaluations. In view of the exploratory nature of these analyses, any p-values reported will not be adjusted for multiple comparisons, and any such analyses will be stated carefully as being hypothesis-generating. All eligible patients who have initiated treatment will be included in the toxicity assessments.

9.4 Reporting and Exclusions

9.4.1 Evaluation of Toxicity

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

9.4.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. 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

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the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses 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.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

10.1.1 CAEPRs for Atezolizumab (MPDL3280A, NSC 783608)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

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

Version 2.5, November 18, 2024[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	Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia)	
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	

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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%)**	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
		Endocrine disorders - Other (thyroiditis)[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			
Fatigue	Fever[3]		***Fatigue (Gr 2)***
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis [immune related hepatitis])[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS))[2]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			

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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%)**	
	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		
	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]	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Guillain-Barre syndrome[2]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (facial paresis)[2]	
		Nervous system disorders - Other (immune-mediated myelitis)[2]	
		Nervous system disorders - Other (meningitis non-infective)[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]	

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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%)**	
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 with systemic symptoms (DRESS))[2]	
		Skin and subcutaneous tissue disorders - Other (Exanthematous pustulosis)[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	
VASCULAR DISORDERS			
		Vascular disorders - Other (immune-mediated vasculitis)[2]	

*Denotes adverse events that are <3%.

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

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

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

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

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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 adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.2 CAEPRs for Tiragolumab (RO7092284; NSC# 827799)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1029 patients.* Below is the CAEPR for Tiragolumab (RO7092284).

> **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.

Version 2.1, November 4, 2024[1]

Adverse Events with Possible Relationship to Tiragolumab (RO7092284) (CTCAE 5.0 Term) [n= 1029]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	

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Adverse Events with Possible Relationship to Tiragolumab (RO7092284) (CTCAE 5.0 Term) [n= 1029]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (autoimmune hemolytic anemia)	
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (immune-mediated pericardial disorders)[3]	
		Myocarditis[3]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[3]	
		Endocrine disorders - Other (diabetes mellitus (Type I))[3]	
		Endocrine disorders - Other (immune-mediated hypophysitis)[3]	
	Hyperthyroidism[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Eye disorders - Other (immune-mediated ocular inflammatory toxicity)[3]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis		
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[3]	
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (immune-mediated hepatitis)[3]		
IMMUNE SYSTEM DISORDERS			
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2,3]	
INFECTIONS AND INFESTATIONS			
		Epstein-Barr virus infection reactivation[2]	
		Infection[4]	
		Lung infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***

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Adverse Events with Possible Relationship to Tiragolumab (RO7092284) (CTCAE 5.0 Term) [n= 1029]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	GGT increased		***GGT increased (Gr 2)***
	Lipase increased		***Lipase increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		
	Serum amylase increased		***Serum amylase increased (Gr 2)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypoalbuminemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
		Rhabdomyolysis[3]	
NERVOUS SYSTEM DISORDERS			
		Nervous system disorders - Other (immune-mediated meningoencephalitis)[3]	
		Nervous system disorders - Other (immune-mediated facial paresis)[3]	
	Peripheral sensory neuropathy		
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (immune-mediated nephritis)[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
		Productive cough	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Pruritus		***Pruritus (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (pemphigoid)	
		Skin and subcutaneous tissue disorders - Other (immune-mediated severe cutaneous adverse reactions (SCARs))[3]	

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Adverse Events with Possible Relationship to Tiragolumab (RO7092284) (CTCAE 5.0 Term) [n= 1029]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Skin and subcutaneous tissue disorders - Other, specify (rash)[5]			***Skin and subcutaneous tissue disorders - Other, specify (rash)[5] (Gr 2)***
VASCULAR DISORDERS			
		Vascular disorders - Other (immune-mediated vasculitis)[3]	

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

[2]In one study of tiragolumab in combination with atezolizumab, a patient with a rare type of lung cancer called lymphoepithelioma-like carcinoma died as the result of reactivation of an Epstein-Barr virus (EBV) infection and hemophagocytic lymphohistiocytosis. The exact cause of the patient's illness is unknown, but the patient's rare type of lung cancer is associated with EBV, and the virus may have come back with treatment with tiragolumab and atezolizumab. Because of this patient's medical history and the timing of the study treatments relative to the illness, tiragolumab and/or atezolizumab may have also contributed to the illness. No other patient treated to date with either tiragolumab alone or in combination with atezolizumab has developed this illness.

[3]Because tiragolumab is designed to serve as an immune checkpoint inhibitor, it is possible that the immune system may cause inflammation not only in the tumor but also in normal tissue. Immune related adverse events, as seen with other drugs stimulating the immune system (for example, atezolizumab) may affect all parts of the body, including (but not limited to) the skin, eyes, nerves, gut, hormone system, kidneys, lungs, liver, muscles, blood vessels, and blood cells. This can cause damage to the normal tissue. Immune related adverse events that have occurred with similar drugs to fight cancer have for the most part been reversible, though some have been permanent, and rarely life threatening or fatal.

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

[5]Rash includes rash maculo-papular, rash erythematous, and immune-mediated rash.

[6]One patient in a prior study with tiragolumab given alone developed a severe case of liver injury and died as the result of liver failure 29 days after receiving one dose of tiragolumab. Given the timing of the illness and considering that no other clear cause could be identified, tiragolumab might have contributed to the liver failure. Your study doctor will monitor your liver function with blood tests throughout the study.

[7]Identified risk when used in combination with atezolizumab.

Adverse events reported on Tiragolumab (RO7092284) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Tiragolumab (RO7092284) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Cardiac arrest; Pericardial tamponade; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
GASTROINTESTINAL DISORDERS - Abdominal distension; Enterocolitis; Esophageal varices hemorrhage; Gastric hemorrhage; Gastrointestinal disorders - Other (peritonitis); Mucositis oral; Small intestinal obstruction; Upper gastrointestinal hemorrhage

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GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Fever; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Pain
HEPATOBILIARY DISORDERS - Gallbladder obstruction; Hepatic failure[6]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall
INVESTIGATIONS - Blood bilirubin increased; Cardiac troponin T increased; Creatinine increased; Investigations - Other (hypertransaminasemia)
METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hypercalcemia; Hypermagnesemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Muscle weakness lower limb; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dizziness; Dysesthesia; Encephalopathy; Guillain-Barre syndrome; Headache; Intracranial hemorrhage; Nervous system disorders - Other (neuromyotonia); Peripheral motor neuropathy; Seizure; Stroke; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Insomnia; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Dyspnea; Epistaxis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (immune-mediated lung disease); Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (carotid artery stenosis)

Note: Tiragolumab (RO7092284) 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.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 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 website 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 10.1) 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 10.3.4.
- **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.

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- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs 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 website:

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- 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.

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 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 as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

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

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** SAEs, 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

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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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

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

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs 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 notifications are required for all SAEs followed by a complete report
- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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.

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10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. The listed AEs are excluded from expedited reporting regardless of whether they result in ≥24h hospitalization of a patient. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade
Investigations	Lymphocyte count decreased	Any
Skin and subcutaneous tissue disorders	Alopecia	Any
Blood and lymphatic system disorders	Anemia	2

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CTCAE SOC	Adverse Event	Grade
Metabolism and nutrient disorders	Hypoalbuminemia; hyperglycemia; hyperuricemia; hypernatremia; hyponatremia; hypokalemia; hypophosphatemia; hypomagnesemia; blood lactate dehydrogenase increased; hypocalcemia; hypercalcemia; alkaline phosphatase increased; hypoalbuminemia	2
Investigations	INR increased; activated partial thromboplastin time prolonged	2

10.3.5 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Adverse events of special interest for this study are as follows:

Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law

- Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
- Treatment-emergent ALT or AST > 3 × ULN 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.

Atezolizumab AESIs

- Immune system disorders, other, specify: systemic lupus erythematosus
- Renal and urinary disorders, other, specify: nephritis
- Ocular toxicities (*e.g.*, uveitis, retinopathy)
- Grade ≥2 cardiac disorders (*e.g.*, atrial fibrillation, myocarditis, pericarditis)
- Events suggestive of allergic reaction, infusion-related reactions, cytokine release syndrome, immune system disorders, (other, specify: macrophage activating syndrome) and immune system disorders, (other, specify: hemophagocytic lymphohistiocytosis)
- Vasculitis
- Autoimmune Hemolytic Anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

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Tiragolumab AESIs

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10xULN
- Immune system disorders, other, specify: systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and infections and infestations, other, specify: meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, and immune system disorders, (other, specify: macrophage activating syndrome) and immune system disorders, (other, specify: hemophagocytic lymphohistiocytosis)
- Renal and urinary disorders, other, specify: nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Myelitis and Facial Paresis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Hemolysis
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

10.4 Routine Adverse Event Reporting

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

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

10.5 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 5 months (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

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"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.

10.6 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 following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

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

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

10.7 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.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 8 days within enrollment and start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If > 8 days have passed since the screening evaluations, the medical history, physical examination, and laboratory evaluations must be repeated prior to starting protocol therapy. Scans and x-rays must be done ≤ 28 days prior to the start of therapy.

A new cycle may begin 1 day earlier or up to 8 days later than it would otherwise be scheduled to allow for flexibility for days the clinic is closed and other unexpected events. Required exams/labs and treatments within a cycle may be adjusted up to +/- 1 day to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle. The research team may perform additional safety/monitoring tests as clinically indicated.

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	Pre-Study Eligibility Screening	**Baseline Clinical Evaluation**	**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4 Wk 1 Onward**	**Progre-ssion/ Response**	**Off Study[a]**
			Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3			
Atezolizumab[a]			X			X			X			X		
Tiragolumab[a]			X			X			X			X		
Informed consent	X													
Demographics	X													
Medical history	X	X[k]	X			X			X			X	X	
Concurrent meds	X	X[k]	X----------										----------X	
Physical exam[b]	X	X[k]	X			X			X			X	X	X
Vital signs	X	X[k]	X			X			X			X	X	X
Height	X	X[k]												
Weight	X	X[k]	X			X			X			X		X
Performance status	X	X[k]				X			X			X	X	X
CBC w/diff, plts[c]	X	X[k]	X[d]			X[d]			X[d]			X[d]	X[d]	X
Serum chemistry[c]	X	X[k]	X[d]			X[d]			X[d]			X[d]	X[d]	X
β-HCG[e,n]	X	X[k]												
Urinalysis[f]	X	X[k]												
EKG[g]	X	X[k]												
Echocardiogram	X	X[k]												
AE evaluation			X----------										----------X	X
Tumor measurements	X	X[k,m]										X[m]		X
Tumor biopsy		X							X				X[h]	
Blood for CTCs[i]			X			X			X			X	X	
Blood for cfDNA[j]			X			X			X			X	X	
Blood for germline			X											

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genomic analysis[l]														
PT/PTT/INR[o]		X[o]								X[o]			X[p]	

a: Each treatment cycle is 21 days long. Atezolizumab will be administered IV at 1200 mg on day 1 of each cycle. Tiragolumab will be administered IV at 600 mg on day 1 of each cycle. Start of the next cycle may be delayed for up to 8 days to accommodate scheduling conflicts.

b: History and physical at baseline and up to 8 days before the start of each subsequent cycle.

c: Serum chemistry (ACTH, albumin, alkaline phosphatase, amylase, AM cortisol, total bilirubin, BUN, calcium, chloride, creatinine, LDH, lipase, phosphorus, total protein, SGOT [AST], SGPT [ALT], magnesium, potassium, and sodium, free T4, TSH) CBC w/ diff, platelets at baseline and at the start of each subsequent cycle (up to 3 days before start of a new cycle). If clinically indicated, labs may be obtained more frequently with subsequent cycles, e.g., CBC w/ diff weekly for grade 3-4 hematologic toxicity.

d: After baseline, amylase, LDH, lipase, total protein, and free T4 do not need to be checked, unless clinically indicated.

e: Urine pregnancy test for women of childbearing potential.

f: Urine chemistry will be performed at eligibility screening and as clinically indicated thereafter.

g: EKG will be performed at eligibility screening and as clinically indicated thereafter.

h: Optional tumor biopsy at progression/response.

i: Mandatory blood for circulating tumor cells (CTCs) will be collected on Day 1 of every cycle (± 3 days for scheduling conflicts) as specified in Section 5.3.3.

j: Mandatory blood for cfDNA will be collected on Day 1 of every cycle (± 3 days for scheduling conflicts) as specified in Section 5.3.3.

k: Values from eligibility screening tests may be used for baseline evaluation values if the test was performed within 8 days of start of protocol therapy (for tumor measurement and ECHO, within 28 days of start of protocol therapy). See Section 3.4 and Section 6.

l: Blood for analysis of germline genomic variants (mandatory) will be collected on Cycle 1, Day 1 for comparison with whole-exome sequencing analysis of tumor tissue as specified in Section 5.3.3.

m: Tumor measurements will be repeated at the end of cycle 3, then every 2 cycles (every 3 cycles for patients on study for >1 years, and every 4 cycles for patients on study >3 years). Documentation (radiologic) must be provided for patients removed from study for progressive disease

n: Additional urine pregnancy testing will be performed as clinically indicated.

o: For patients undergoing mandatory biopsy collection: Prothrombin time (PT), partial thromboplastin time (PTT), or international normalized ratio (INR) test at baseline and prior to Cycle 3, Day 1.

p: For patients undergoing optional biopsy collection only.

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12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at the end of cycle 3, then every 2 cycles (every 3 cycles for patients on study for >1 years, and every 4 cycles for patients on study >3 years. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [71]. 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.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab and tiragolumab.

Evaluable for Objective Response. All eligible patients who have initiated treatment will be evaluable for response. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 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).

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,

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and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

12.1.3 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.

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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 following complete response (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) and PSA response (in recurrent prostate cancer) have been published [72-74]. 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 .

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

12.1.4 Response Criteria

12.1.4.1 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,

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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.

12.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 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-	No	PR	

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	PD/not evaluated			
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

12.1.5 Duration of Response

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

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

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

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12.1.6 Progression-Free Survival

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

12.2 Antitumor Effect – Immune-Related RECIST (iRECIST) Criteria

Overall response will also be assessed using iRECIST as an exploratory endpoint, for comparison to RECIST v1.1.

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. Investigators should continue treatment, as appropriate, in the absence of unacceptable toxicity, until unequivocal disease progression. This is particularly important for patients in whom pseudoprogression may have occurred. Follow up response assessments must be continued until unequivocal disease progression has occurred.

The iRECIST criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately. Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
    - Continued unequivocal progression in non-target disease with an increase in tumor burden.
    - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that

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iCPD is not documented at the next assessment after iUPD (*Lancet Oncol* 18:e143-e152, 2017 - Table 2).

New lesions:

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]), and recorded as New Lesions - Target (NLT) and New Lesion - Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Time-point (TP) iResponse

Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Time Point Response**	
			No prior iUPD**	**Prior iUPD**, *****
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD.
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD).

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Time-point (TP) iResponse

Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Time Point Response**	
			No prior iUPD**	**Prior iUPD**, *****
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD.
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and/or • previously identified NT lesion iUPD (need not be unequivocal) and/or • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified.
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR, and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

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iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Table assumes a randomized study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

12.3 Treatment Beyond RECIST Progression

During treatment, patients who show evidence of clinical benefit will be permitted to continue atezolizumab and tiragolumab treatment following progression (as defined by RECIST v1.1), as long as the increase in disease burden does not meet the definition of confirmed PD by immune response criteria and if they meet all of the following additional criteria:

- Evidence of clinical benefit as assessed by the investigator and agreed upon by the Medical Monitor
- Absence of symptoms or signs (including worsening laboratory values) indicating unequivocal progression of disease
- No significant decline in performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The investigator must discuss with the patient the risks and benefits of treatment continuation

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after possible worsening disease and must document the patient's agreement to continue receiving atezolizumab in the medical record.

If the investigator and patient decide to continue treatment, confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after the assessment in which the RECIST 1.1 definition of PD was met. If this consecutive scan confirms PD, the patient should come off treatment.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

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

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

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

13.2 Data 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, 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.

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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 or Rave SLA role must have at a minimum an Associate (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals 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 the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

13.2.1 Method

*For studies assigned for **CTMS Routine** Monitoring:*

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding

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data quality or timely submission. 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.

13.2.2 Responsibility for Data Submission

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

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

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

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

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

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

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13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.4 CTEP Multicenter Guidelines

N/A

13.5 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.

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Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and

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

Email: ncicteppubs@mail.nih.gov

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

13.6 Genomic Data Sharing Plan

The NIH Genomic Data Sharing (GDS) Policy ensures broad and responsible sharing of genomic research data from all NIH-funded research (https://gds.nih.gov/index.html). Providing that patient consent has been obtained, targeted sequencing, whole-exome sequencing, and RNA-seq data generated for research purposes from de-identified samples will be submitted to the Database of Genotypes and Phenotypes (dbGaP) for controlled-access use within a time frame consistent with data publication. The identities of research participants will not be disclosed to dbGaP or to secondary users of the data.

13.7 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
x De-identified data in an NIH-funded or approved public repository
x Identified data in BTRIS (automatic for activities in the Clinical Center)
x De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
x An NIH-funded or approved public repository: clinicaltrials.gov
x BTRIS (automatic for activities in the Clinical Center)
x Approved outside collaborators under appropriate individual agreements
x Publication and/or public presentations

When will the data be shared?
x At the time of publication or shortly thereafter

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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.

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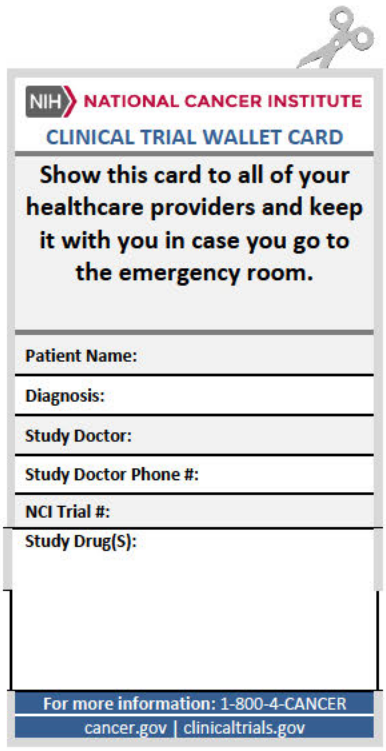
APPENDIX B PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

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APPENDIX C RARE TUMOR ELIGIBILITY LIST

This list of histologic subtypes was adapted from DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (NCT#02834013) (SWOG S1609); see http://www.swogstat.org/accrual/dart.pdf; rare cancers are defined per RARECARE as those with an incidence of fewer than 6 cases per 100,000 people per year.

Note: Subtypes from #54 on were excluded from DART due to existing evaluations of combination immune checkpoint blockade in these histologies. Only solid tumors will be included.

1. Epithelial tumors of nasal cavity, sinuses, nasopharynx
2. Epithelial tumors of major salivary glands
3. Salivary gland type tumors of head and neck, lip, esophagus, stomach, trachea and lung, breast and other location
4. Undifferentiated carcinoma of gastrointestinal (GI) tract
5. Adenocarcinoma with variants of small intestine
6. Squamous cell carcinoma with variants of GI tract (stomach small intestine, colon, rectum, pancreas)
7. Fibromixoma and low-grade mucinous adenocarcinoma (pseudomixoma peritonei) of the appendix and ovary
8. Rare Pancreatic tumors including acinar cell carcinoma, mucinous cystadenocarcinoma or serous cystadenocarcinoma
9. Intrahepatic cholangiocarcinoma
10. Extrahepatic cholangiocarcinoma and bile duct tumors
11. Sarcomatoid carcinoma of lung
12. Bronchoalveolar carcinoma lung (a.k.a. adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma, or invasive mucinous adenocarcinoma)
13. Non-epithelial tumors of the ovary
14. Trophoblastic tumor
15. Transitional cell carcinoma other than that of the renal, pelvis, ureter, or bladder
16. Cell tumor of the testes and extragonadal germ tumors
17. Epithelial tumors of penis - squamous adenocarcinoma cell carcinoma with variants of penis
18. Squamous cell carcinoma variants of the genitourinary (GU) system
19. Spindle cell carcinoma of kidney, pelvis, ureter
20. Adenocarcinoma with variants of GU system (excluding prostate cancer)
21. Odontogenic malignant tumors
22. Pancreatic neuroendocrine tumor (PNET)
23. Neuroendocrine carcinoma including carcinoid of the lung
24. Pheochromocytoma, malignant
25. Paraganglioma
26. Carcinomas of pituitary gland, thyroid gland parathyroid gland and adrenal cortex
27. Desmoid tumors
28. Peripheral nerve sheath tumors and NF1-related tumors
29. Malignant giant cell tumors
30. Chordoma

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31. Adrenal cortical tumors
32. Tumor of unknown primary (Cancer of Unknown Primary; CuP)
33. Not Otherwise Categorized (NOC) Rare Tumors, after discussion with Study Chairs
34. Adenoid cystic carcinoma
35. Vulvar cancer
36. MetaPLASTIC carcinoma (of the breast)
37. Gastrointestinal stromal tumor (GIST)
38. Perivascular epithelioid cell tumor (PEComa)
39. Apocrine tumors/Extramammary Paget's Disease
40. Peritoneal mesothelioma
41. Basal cell carcinoma
42. Clear cell cervical cancer
43. Esthenioneuroblastoma
44. Endometrial carcinosarcoma (malignant mixed Mullerian tumors)
45. Clear cell endometrial cancer
46. Clear cell ovarian cancer
47. Gestational trophoblastic disease (GTD)
48. Gallbladder cancer
49. Small cell carcinoma of the ovary, hypercalcemic type
50. Angiosarcoma
51. High-grade neuroendocrine carcinoma
52. Treatment-emergent small-cell neuroendocrine prostate cancer (t-SCNC)
53. Anal cancer
54. Lymphoma
55. Merkel cell carcinoma
56. Pleural Mesothelioma
57. Sarcoma, other
58. Thymic Carcinoma
59. Uterine Leiomyosarcoma
60. Papillary RCC

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