NEO-ADJUVANT ATEZOLIZUMAB PRIOR TO DEFINITIVE SURGICAL RESECTION OF REGIONALLY METASTATIC HEAD & NECK CUTANEOUS SQUAMOUS CELL CARCINOMA WITH AN UNKNOWN OR HISTORIC PRIMARY SITE: A WINDOW TRIAL

Protocol Number:	UCDCC#295
Indication:	Neo-adjuvant Atezolizumab prior to definitive surgical resection of regionally metastatic head & neck cutaneous squamous cell carcinoma with an unknown or historic primary site: a window trial
Phase:	II
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Principal Investigator / Sponsor Contact:	Arnaud Bewley, MD University of California, Davis Department of Otolaryngology / Head and Neck Surgery 2521 Stockton Blvd, Suite 7200, Sacramento, CA 95817 Ph: 916-734-2790 / Fax: 916-734-5011 / Email: abewley@ucdavis.edu
Co-Investigator(s):	Andrew Birkeland, MD University of California, Davis Department of Otolaryngology/Head and Neck Surgery 2521 Stockton Blvd, Suite 7200, Sacramento, CA 95817 Ph: 916-734-2790/ Fax: 916-734-5011 / Email: acbirkeland@ucdavis.edu Jonathan Riess, MD University of California, Davis Division of Hematology/Oncology Ph: 916-734-3772 / Fax: 916-734-7946 / Email: jwriess@ucdavis.edu
Statistician:	Heejung Bang, PhD Division of Biostatistics University of California, Davis One Shields Avenue, Davis, CA 95616 Email: hbang@ucdavis.edu
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PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#295

Protocol Title: *Neo-adjuvant anti-PD-L1 therapy prior to definitive surgical resection of regionally metastatic head & neck cutaneous squamous cell carcinoma with an unknown or historic primary site: a window trial*

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

PROTOCOL SYNOPSIS

Protocol Title

Neo-adjuvant Atezolizumab prior to definitive surgical resection of regionally metastatic head and neck cutaneous squamous cell carcinoma with an unknown or historic primary site.

Protocol Number

UCDCC#295

Phase of Development

II

Investigational Product, Dosage Form, Route, and Dose Regimen

Neoadjuvant prior to definitive surgery: atezolizumab 1200 mg IV Q3 weeks x 2 cycles

Adjuvant: atezolizumab 1200 mg IV Q3 weeks x 15 cycles (in combination with radiation therapy)

Primary Objective

Evaluate the rate of pathologic complete response (pCR) at the time of surgery following neo-adjuvant atezolizumab in patients with regionally metastatic head and neck cutaneous squamous cell carcinoma (HNSCCC):

Secondary Objectives

1) Further characterize the oncologic response to neo-adjuvant atezolizumab and adjuvant atezolizumab in combination with radiation therapy in patients with regionally metastatic head and neck cutaneous squamous cell carcinoma (HNSCCC):

a) Determine the rate of major pathologic response (mPR) at the time of surgery.
b) Evaluate the 2-year event free survival (EFS) after completion of adjuvant therapy.

2) Investigate the utility of conventional imaging and novel biomarkers in predicting and assessing response to neoadjuvant atezolizumab therapy.

a) Investigate associations between pre-treatment tumor FDG avidity and response to neoadjuvant immunotherapy
b) Evaluate the ability of fine-cut contrast enhanced CT or MRI of the head and neck to assess response to neoadjuvant immunotherapy prior to surgery.
c) Evaluate the capabilities of serial liquid biopsy analysis of tumor-associated exosomes to predict neoadjuvant immunotherapy response.

3) Evaluate the safety and tolerability of anti-PD-L1 with atezolizumab neo-adjuvant therapy in resectable regional metastatic HNCSCC.

a) Quantify Toxicity (adverse events) determined by CTCAE v5

Study Design and Investigational Plan / Methodology

This is a Phase II trial investigating the efficacy of the anti-PD-L1 antibody atezolizumab (Tecentriq) in the neoadjuvant setting for patients with regionally metastatic cutaneous head and neck squamous cell carcinoma with a historic or unknown primary. This will be an open-label trial with a single arm reporting response rates with pathologic response (pCR) as the primary endpoint.

Screening

Patients will be screened for eligibility based on their clinical history, imaging and pathology results obtained prior to initial consultation. Patients who meet eligibility criteria will be presented with the details of the study at their initial clinical evaluation. Patients interested in participating in the study will then be consented and enrolled by a member of the study team.

- *Clinical Evaluation*

At initial screening visit, patients will undergo a full history and physical (H&P) and comprehensive bloodwork (SoC). A Fine needle aspiration (FNA) or core needle biopsy will be performed of the involved lymph node if pathologic diagnosis has not yet obtained. Photo-documentation of the regional tumor bed will be performed.

Screening bloodwork will be obtained (See section 5.1.5) and processed through the central laboratory as per routine SoC. In addition, one 4 mL lavender-top tube will be drawn simultaneously with these scheduled blood draws for research analysis of tumor-associated exosomes.

- *Imaging*

Baseline imaging will include fine-cut contrast enhanced CT or MRI of the head and neck and a full body PET/CT. Imaging will not be repeated for patients who have already completed imaging within one month of initial consultation.

Neo-adjuvant Atezolizumab

Atezolizumab 1200 mg will be administered on Day 1 of each 21 day cycle (Q3 weeks = Q3W) in the neoadjuvant period for 2 doses. Patients will then proceed with SoC surgery, the extent dictated by initial presentation of disease status prior to administration of atezolizumab.

Pre-Dose Blood Draws

Participants will undergo blood draws at the infusion center prior to administration of neo-adjuvant atezolizumab for routine blood analysis as noted in section 5.1.5. One 4 mL lavender-top tube will be drawn simultaneously with these scheduled blood draws for research analysis of tumor-associated exosomes.

Post-neo-adjuvant Imaging

Repeat fine-cut contrast-enhanced CT or MRI imaging of the head and neck will be performed one week prior to surgery to assess response to neoadjuvant therapy. The imaging modality utilized will be the same as that modality used for screening.

Surgery and Pathologic Evaluation

All participants will undergo a curative-intent surgical resection as defined by SoC. Surgery will occur within 10 weeks of study enrollment and at least two weeks after second dose of neoadjuvant Atezolizumab. The goal of curative intent surgery for regionally metastatic CSCC involves resection to negative margins of the index lesion with the associated at-risk regional lymph nodes as determined by the study physician. An evaluation of tumor status and staging per AJCC guidelines (8^{th} edition) will be performed on all surgical specimens. The pathologist will assess the specimen for pCR and mPR (see 10.1).

Patients demonstrating pCR at time of surgery:

Adjuvant Treatment

Patient demonstrating pCR at the time of surgery will not receive any additional adjuvant therapy and will enter surveillance.

Imaging

PET/CT will be performed approximately 12 weeks after surgery.

Follow-up / Surveillance

Patients will be followed in otolaryngology/head and neck surgery and medical oncology clinic every 3 months for 3 years after surgery. Patients will be assessed for treatment-related side effects, cancer recurrence and blood draws performed at the cancer center for biomarkers.

In the setting of suspected clinical or radiographic recurrence per iRECIST criteria,

tumor tissue will be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator.

Patients with residual disease at time of surgery:

Patients with residual disease at the time of surgery will receive atezolizumab Q3W x 15 cycles in combination with SoC adjuvant radiation. SoC adjuvant radiation typically begins 6-7 weeks

after surgery and consists of 6 weeks of radiation with dosing dictated by pathologic findings. Recommendations for adjuvant radiation will be determined at a multidisciplinary tumor board where surgical pathology findings will be reviewed. Adjuvant atezolizumab will begin concurrent to adjuvant radiation and continue for 15 cycles.

Pre-Dose Blood Draws

As in the neo-adjuvant setting, participants will undergo blood draws at the infusion center prior to administration of adjuvant atezolizumab for routine blood analysis as noted in section 5.1.5. One 4 mL lavender-top tube will be drawn simultaneously with these scheduled blood draws for research analysis of tumor-associated exosomes.

Imaging

All participants will have imaging performed with PET/CT approximately 12 weeks (+/- 1 week) after completion of adjuvant RT.

Follow-up / Surveillance

Patients will be followed in otolaryngology/head and neck surgery and medical oncology clinic every 3 months for 2 years after completion of adjuvant atezolizumab. Patients will be assessed for treatment-related side effects, cancer recurrence and undergo blood draws for biomarkers.

In the setting of suspected clinical or radiographic recurrence per iRECIST, tumor tissue will be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator.

Study Population & Eligibility Criteria

Participants ≥ 18 years with resectable regionally metastatic HNCSCC from an unknown or historical primary. Patients must have surgically resectable disease and no evidence of distant metastatic spread. Patients cannot have a concurrent identifiable primary tumor and cannot have had previous RT in the area designated for treatment.

Sample Size and Statistical Considerations:

Simon's two-stage design (Simon, 1989) was used to determine sample size. The null hypothesis that the true response rate (pCR) is p0 = 0.05 will be tested against a one-sided alternative. In the first stage, 5 patients will be accrued. If there are no responses in these 5 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 18. The null hypothesis will be rejected if 3 or more responses are observed in 18 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 0.3.

Due to the nature of single arm and small sample size, we will not adjust our analyses for multiplicity but we will present all outcomes we studied in a single paper with a pre-specified designation of each outcome (e.g., primary or secondary/exploratory). Also, formal hypothesis

testing will be avoided or properly accompanied/indicated by a warning (e.g., a historical control for comparator or other comparability issues).

We will summarize continuous data at baseline with standard descriptive statistics, e.g., mean and SD (or median and IQR) and binary data with frequency and proportion. For continuous and binary outcomes data, point estimates and 95% CIs will be computed for appropriate parameter estimable (e.g., mean or median with accounting for censoring, if needed) and the Clopper and Pearson exact binomial method (with no censoring), respectively.

Longitudinal data will be summarized similarly and accompanied by time point to illustrate possible trends. When we utilize historical controls (for description and informal comparison), we will use control sample matched on key confounders (e.g., age, gender, key comorbidities and medical histories). We expect approximately 40 control patients, thus, achieving approximately 1:2 ratio in sample size for current sample: comparator.

Endpoints

Primary Endpoint

pCR

Secondary Endpoints

1) Oncologic response to therapy:

a) MPR
b) 2-year EFS

2) Imaging and biomarker assessment of response to therapy.

a) FDG avidity of nodal disease sites as measured by PET
b) ORR as measured by CT or MRI of the head and neck per iRECIST criteria
c) Plasma exosome levels

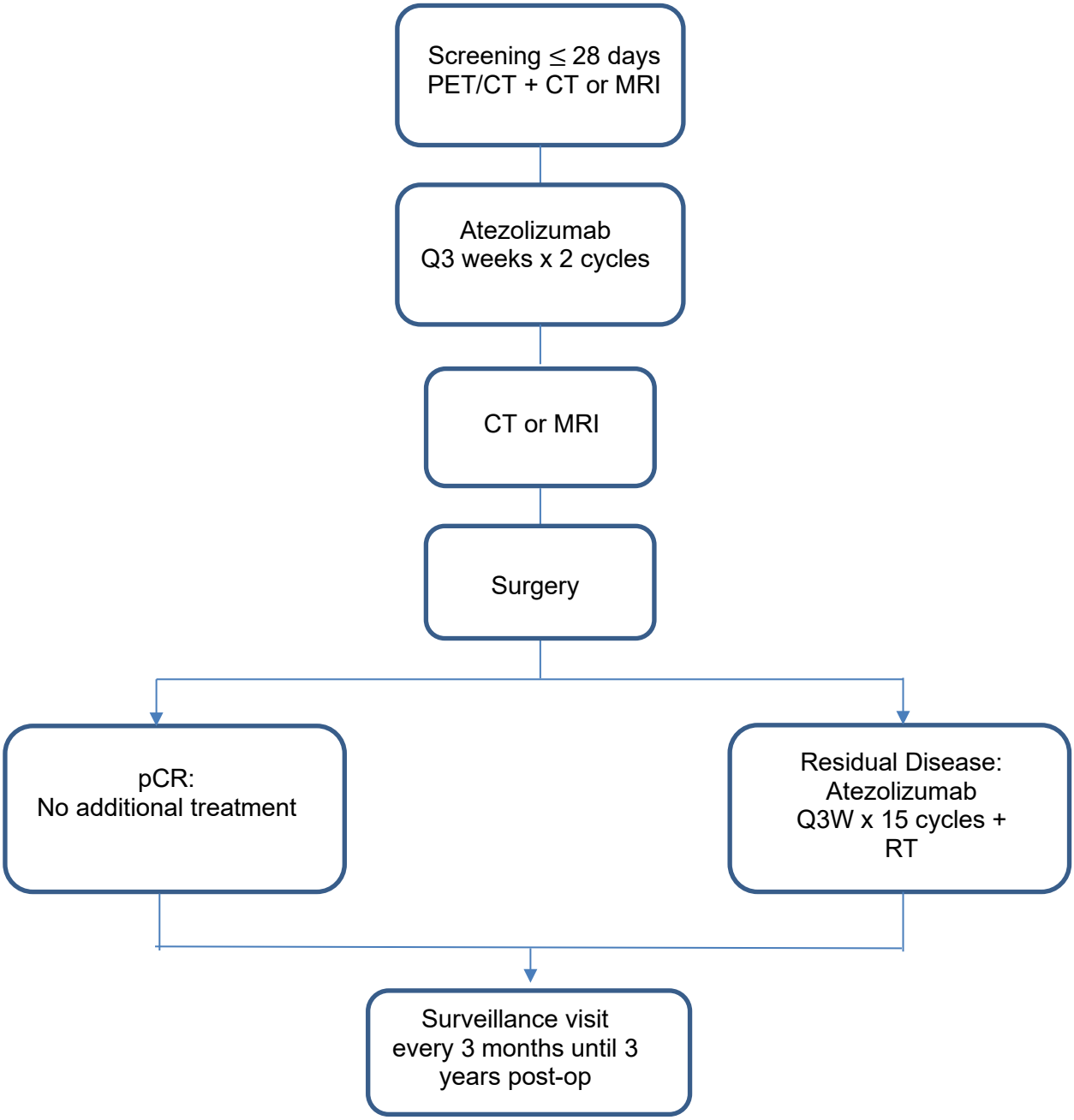
3) Safety and Tolerability assessment:

a) Toxicity (adverse events) determined by CTCAE v5

Duration of Study and Follow-up

We anticipate that it will take approximately two years to accrue the desired 18 patients. Each patient will be followed for a minimum of 2 years after completion of adjuvant atezolizumab. We estimate it will take 2.5 years to achieve our primary endpoint of pCR and 5 years to complete the study in its entirety.

STUDY SCHEMA



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1. INTRODUCTION

1.1 Background and Study Rationale

Head and neck cutaneous squamous cell carcinoma (HNCSCC) remains a challenging disease to treat. In advanced stages, it has poor disease-free survival (DFS) and overall survival (OS) (Harris 2017). Our current treatment options are limited to surgery and radiation, with limited success in advanced and regionally metastatic cases. There is a pressing need to investigate new therapeutic modalities to improve outcomes and survival.

Neoadjuvant immunotherapeutics (anti-PD-1 and anti-PD-L1) antibodies offer significant potential for HNCSCC patients, with opportunities to improve survival and disease extent. Data from a phase II study of neoadjuvant cemiplimab prior to surgery in patients with stage III/IV HNCSCC demonstrated a pCR in 55% of patients and major pathologic response in an additional 15% (Gross 2019). Patients who had a pCR were de-escalated from adjuvant radiation. The high response rate of HNCSCC is thought to be related to their high mutational burden from UV light-mediated DNA damage resulting in highly immune-responsive tumors.

A challenge for recruiting HNCSCC with previous studies for immunotherapeutics has been that many patients present with advanced, regionally metastatic disease with their primary site previously treated by their local provide (surgeon, dermatologist). Thus, these patients with aggressive, regionally metastatic disease with poor outcomes (who would likely benefit from neoadjuvant trials of immunotherapeutics), have not met criteria for any existing phase II & III clinical trials. At UC Davis, we treat a large volume of patients with this disease and have extensively studied their outcomes. Patients with regionally metastatic disease from an occult or historical primary are currently overlooked by existing HNCSCC trials but are seen at a high volume at UC Davis.

Here, we propose to address this overlooked population of regionally metastatic HNCSCC with occult or previous primary, utilizing a regimen of neoadjuvant atezolizumab (Genentech) to assess tumor response in regional nodal disease in addition to adjuvant atezolizumab added to the SoC. The data gleaned from this phase II trial may lead to later stage multicenter clinical trials, novel correlative biomarkers, and improvement and advancement of current care for patients with HNCSCC.

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T−cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see atezolizumab Investigator's Brochure for detailed efficacy results).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment or interruption of atezolizumab treatment.

1.2 Background on Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor–specific T–cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc–effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab is approved for the treatment of certain lung cancers, hepatocellular carcinoma, melanoma, and others.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

Evaluate the rate of pathologic complete response (pCR) at the time of surgery following neo-adjuvant atezolizumab in patients with regionally metastatic head and neck cutaneous squamous cell carcinoma (HNSCCC):

2.2 Secondary Objectives

1) Further characterize the oncologic response to neo-adjuvant atezolizumab and adjuvant atezolizumab in combination with radiation therapy in patients with regionally metastatic HNSCCC:

a) Determine the rate of major pathologic response (mPR) at the time of surgery.
b) Evaluate the 2-year event free survival (EFS) after completion of adjuvant therapy.

2) Investigate the utility of conventional imaging and novel biomarkers in predicting and assessing response to neoadjuvant atezolizumab therapy.

a) Investigate associations between pre-treatment tumor FDG avidity and response to neoadjuvant immunotherapy

b) Evaluate the ability of fine-cut contrast enhanced CT or MRI of the head and neck to assess response to neoadjuvant immunotherapy prior to surgery.
c) Evaluate the capabilities of serial liquid biopsy analysis of tumor-associated exosomes to predict neoadjuvant immunotherapy response.

3) Evaluate the safety and tolerability of anti-PD-L1 with atezolizumab neo-adjuvant therapy in resectable regional metastatic HNCSCC.

a) Quantify Toxicity (adverse events) determined by CTCAE v5

2.2 Endpoints

Primary Endpoint

pCR

Secondary Endpoints

1) Oncologic response to therapy:

a) MPR
b) 2-year EFS

2) Imaging and biomarker assessment of response to therapy.

d) FDG avidity of nodal disease sites as measured by PET
e) ORR as measured by CT or MRI of the head and neck per iRECIST criteria
f) Plasma exosome levels

3) Safety and Tolerability assessment:

a) Toxicity (adverse events) determined by CTCAE v5

3. STUDY DESIGN

3.1 Description of the Study

This is a Phase II trial investigating the efficacy of the anti-PD-L1 antibody atezolizumab (Tecentriq) in the neoadjuvant setting for patients with regionally metastatic cutaneous head and neck squamous cell carcinoma with a historic or unknown primary. This will be an open-label trial with by pCR as the primary endpoint.

Screening

Patients will be screened for eligibility based on their clinical history, imaging and pathology results obtained prior to initial consultation. Patients who meet eligibility criteria will be presented with the details of the study at their initial clinical evaluation. Patients interested in participating in the study will then be consented and enrolled by a member of the study team.

- *Clinical Evaluation*

At initial screening visit, patients will undergo a full history and physical (H&P) and comprehensive bloodwork as per SoC. A Fine needle aspiration (FNA) or core needle

biopsy will be performed of the involved lymph node if pathologic diagnosis has not yet obtained. Photo-documentation of the regional tumor bed will be performed.

Screening bloodwork will be obtained (See section 5.1.5) and processed through the central laboratory as per routine SoC. In addition, one 4 mL lavender-top tube will be drawn simultaneously with these scheduled blood draws for research analysis of tumor-associated exosomes. This research vial will be transported by Dr. Birkeland, Dr. Bewley, Angela Beliveau, or other approved Otolaryngology department members to the Cancer Center Biorepository for cataloging (contact: Irmgard Feldman), and storage as needed. Collected whole blood samples will be withdrawn and processed by Dr. Birkeland and collaborators when needed for subsequent analysis.

- *Imaging*

Baseline imaging will include fine-cut contrast enhanced CT or MRI of the head and neck and a full body PET/CT. Imaging will not be repeated for patients who have already completed imaging within one month of initial consultation.

Neo-adjuvant Atezolizumab

Atezolizumab 1200 mg will be administered on Day 1 of each 21 day cycle (Q3 weeks = Q3W) in the neoadjuvant period for 2 cycles (cycle length = 21 days). Patients will then proceed with SoC surgery, the extent dictated by initial presentation of disease status prior to administration of atezolizumab.

Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, clinical or radiographic progression per iRECIST may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients with clinical or radiographic evidence of progression while receiving neo-adjuvant atezolizumab will be permitted to receive their second dose and postoperative adjuvant doses of atezolizumab if they meet <u>all</u> of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of 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

Patient who have NOT met all of the above criteria will NOT receive their second dose of neo-adjuvant atezolizumab and will proceed directly to surgery. These patients will also not receive adjuvant atezolizumab and will receive only SoC adjuvant radiation.

Pre-Dose Blood Draws

Participants will undergo blood draws at the infusion center prior to administration of neo-adjuvant atezolizumab for routine blood analysis as noted in section 5.1.5. One 4 mL lavender-top tube will be drawn simultaneously with these scheduled blood draws for research analysis of tumor-associated exosomes. This research vial will be transported by Dr. Birkeland, Dr. Bewley Angela Beliveau, or other approved Otolaryngology department members to the Cancer Center Biorepository for cataloging (contact: Irmgard Feldman), and storage as needed. Collected whole blood samples will be withdrawn and processed by Dr. Birkeland and collaborators when needed for subsequent analysis.

Post-neo-adjuvant Imaging

Repeat fine-cut contrast-enhanced CT or MRI imaging of the head and neck will be performed one week prior to surgery to assess response to neo-adjuvant therapy. The imaging modality utilized will be the same as that modality used for screening.

Surgery and Pathologic Evaluation

All participants will undergo a curative-intent surgical resection as defined by SoC. Surgery will occur within 10 weeks of study enrollment and at least two weeks after second dose of neoadjuvant Atezolizumab. The goal of curative intent surgery for regionally metastatic CSCC involves resection to negative margins of the index lesion with the associated at-risk regional lymph nodes as determined by the study physician. An evaluation of tumor status and staging per AJCC guidelines (8^{th} edition) will be performed on all surgical specimen. The pathologist will assess the specimen for pCR and mPR (see 10.1). Pathology assessment will be as per standard of care documentation, including: dimensions of index lesion, total nodal number of lymph nodes removed, total positive node number (and positive nodal levels), any extracapsular extension, any perineural invasion. PD-L1 staining will be performed on a representative section from the largest positive node. Tissue will be formalin fixed and paraffin embedded and banked per standard pathology protocol.

Patients demonstrating pCR at time of surgery:

Adjuvant Treatment

Patients demonstrating pCR at the time of surgery will not receive any additional adjuvant therapy and will enter surveillance.

Imaging

PET/CT will be performed approximately 12 weeks after surgery.

Follow-up / Surveillance

Patients will be followed in otolaryngology/head and neck surgery and medical oncology clinic every 3 months for 3 years after surgery. Patients will be assessed for treatment-related side effects, cancer recurrence and blood draws performed at the cancer center for biomarkers.

In the setting of suspected clinical or radiographic recurrence per iRECIST criteria, tumor tissue will be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator.

Patients with residual disease at time of surgery:

Patients with residual disease at the time of surgery will receive atezolizumab Q3W x 15 cycles in combination with SoC adjuvant radiation. SoC adjuvant radiation will be initiated greater than 4 weeks and less than 7 weeks after surgery and consists of 6 weeks of radiation therapy with dosimetry determined by pathologic findings at the time of surgery. Recommendations for adjuvant treatment will be determined at a multidisciplinary tumor board where surgical pathology findings will be reviewed. Adjuvant atezolizumab will begin concurrent to adjuvant radiation and continue for 15 cycles.

Pre-Dose Blood Draws

As in the neo-adjuvant setting, participants will undergo blood draws at the infusion center prior to administration of adjuvant atezolizumab for routine blood analysis as noted in section 5.1.5. One 4 mL lavender-top tube will be drawn simultaneously with these scheduled blood draws for research analysis of tumor-associated exosomes. This research vial will be transported by Dr. Birkeland, Dr. Bewley, Angela Beliveau, or other approved Otolaryngology department members to the Cancer Center Biorepository for cataloging (contact: Irmgard Feldman), and storage as needed. Collected whole blood samples will be withdrawn and processed by Dr. Birkeland and collaborators when needed for subsequent analysis.

Imaging

All participants will have imaging performed with PET/CT approximately 12 weeks after completion of adjuvant RT.

Follow-up / Surveillance

Patients will be followed in otolaryngology/head and neck surgery and medical oncology clinic every 3 months for 2 years after completion of adjuvant atezolizumab. Patients will be assessed for treatment-related side effects, cancer recurrence and blood draws for biomarker. In the setting of suspected clinical or radiographic recurrence per iRECIST, tumor tissue will be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator.

3.2 End of Study and Length of Study

The end of this study is defined as the date when the last patient has completed their neoadjuvant atezolizumab doses and completed their definitive surgery, any adjuvant treatment and two (patients receiving adjuvant therapy) or three (patient no receiving adjuvant therapy) years of clinical follow-up. The end of the study is expected to occur within 36 months of the last patient being enrolled. The total length of the study, from screening of the first patient to the end of the study, is therefore expected to be approximately 60 months. In addition, the Investigator may decide to terminate the study at any time.

3.3 Rationale for Study Design

Primary surgical resection of regionally metastatic cutaneous squamous cell carcinoma can result in severe functional and cosmetic morbidity due to involvement of overlying skin and underlying cranial nerves. These patients also suffer from higher rates of regional and distant metastatic failure than other patients with advanced CSCC (Harris 2019). A neoadjuvant approach to treatment offers the potential to 1) reduce morbidity associated with primary surgical resection and 2) improve oncologic outcomes. Our neoadjuvant study design also provides an appealing “window of opportunity” to correlate serum and pathologic biomarkers to immunotherapy response.

3.3.1 Rationale for Imaging protocol

Fine-cut contrast-enhanced CT or MRI of the head and neck.

Pre-treatment fine-cut contrast enhanced cross sectional imaging of the head neck is SoC for any patient diagnosed with advanced head and neck cancer. Repeating imaging after neoadjuvant therapy and prior to surgery will provide a unique opportunity to correlate response

to immunotherapy as measured by iRECIST criteria with objective pathologic data at minimal additional risk to the patient.

PET/CT

SoC staging PET/CT will be performed prior to initiation of treatment and as a post-treatment scan 3 months after completion of surgery or surgery + RT.

3.3.2 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W in both the neo-adjuvant and adjuvant setting, which is the approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.3.3 Rationale for Patient Population

This study will enroll patients with regionally metastatic cutaneous head and neck squamous cell carcinoma with a historical or unknown primary. The prognosis for patients with regionally metastatic cutaneous head and neck squamous cell carcinoma poor. In our institution, a cohort of patients with regionally metastatic or recurrent cutaneous SCC had a 5-year disease free survival of 53.2% (Harris et al. 2017). Regional nodal disease confers a hazard ratio of over 2 for both disease free survival and overall survival in these patients (Harris et al. 2019). Current treatment options are limited primarily to surgery and radiation, with limited if any benefit from traditional cytotoxic chemotherapies. Approved therapies are associated with significant toxicities (e.g., surgical wounds, radiation toxicity) that negatively impact quality of life. Therefore, there is a continuing need for more efficacious, better-tolerated treatments.

Inhibition of PD-L1/PD-1 signaling has been recently shown to have significant benefit in a variety of tumors, including cutaneous SCC. However, there is a need for further investigation as to its effects in regionally metastatic cutaneous SCC. Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients in several tumor types (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). Atezolizumab monotherapy is generally well tolerated in cancer patients (Besse et al. 2015; Horn et al. 2015; Spigel et al. 2015; Fehrenbacher et al. 2016).

3.3.4 Rationale for Control Group

We will be comparing trial patients with historical controls from our institution, as previously collected and published (Harris et al. 2017 and Harris et al. 2019). Our rationale is that there stands to be significant treatment benefits for such patients, and current survival outcomes with SoC is well-documented.

3.3.5 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor

types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow all patients to continue treatment after apparent radiographic progression per iRECIST, provided the benefit-risk ratio is judged to be favorable by the investigator and the patient agrees to continue treatment. Notably, patients are only receiving two neoadjuvant doses of atezolizumab in this study. Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status.

3.3.6 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected where available from patients and tested for PD-L1 expression by a central laboratory. Tumor tissue will be collected from definitive surgical specimens. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Archival tumor tissue will be collected at baseline where available. Tumor tissue will be collected from definitive surgical specimens. Tumor tissue will also be collected by biopsy at the time of first evidence of radiographic disease progression per iRECIST, if deemed clinically feasible by the investigator, to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as exosome levels and content, expression marker changes on exosomes, and cytokines associated with T-cell activation and lymphocyte subpopulations may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

4. SUBJECT SELECTION

Participants with biopsy proven, surgically resectable head and neck cutaneous squamous cell carcinoma regionally metastatic to lymph nodes in the head and/or neck with a historical or unknown (but not concurrent) primary site, are eligible to be **included** only if all the following:

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry.

1. Patients must be $\geq$ 18 years
2. Patients with resectable regionally metastatic HNCSCC from an unknown or historical primary and no evidence of distant metastatic disease.
3. Full decision-making capacity and consent provided and documented.
4. Radiographically measurable disease per iRECIST
5. Surgically resectable disease per SoC.

6. For Women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods as defined below:
    - Women must remain abstinent or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 5 months after the final dose of atezolizumab.
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    - Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
7. Men: abstinent or using effective contraception method
8. Tumor tissue sample adequate for PD-L1 and biomarker studies
9. ECOG performance status 0 or 1 (Section 15.1).
10. Availability of a representative tumor specimen for exploratory biomarker research (see Section 5.1.5 for information on tumor specimens)
11. Life expectancy $\geq$ 2 years
12. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
    - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
    - Platelet count $\geq 50 \times 10^9$/L (50,000/μL) without transfusion
    - Hemoglobin $\geq$ 80 g/L (8 g/dL)
        - Patients may be transfused to meet this criterion.
    - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:
    - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:
        - Patients with known Gilbert disease: serum bilirubin $\leq 3 \times$ ULN
    - Serum creatinine $\leq 1.5 \times$ ULN
    - Serum albumin $\geq$ 25 g/L (2.5 g/dL)
13. For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
14. For patients receiving therapeutic anticoagulant regimen

15. Negative HIV test at screening with the following exception: patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count ≥ 200, and have an undetectable viral load
16. Negative hepatitis B surface antigen (HBsAg) test at screening
17. Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening
18. The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Distant metastatic disease
2. Unresectable disease: As defined by: common or internal carotid artery encasement or involvement of the skull base involvement or pre-vertebral fascia
3. Uncontrolled tumor-related pain
4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
    - Patients with indwelling catheters (e.g., PleurX®) are allowed.
5. Uncontrolled (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia
6. Active or history of autoimmune disease or immune deficiency (see Section 15.9), including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:
    - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover < 10% of body surface area
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
        - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
    - Any history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
7. Known active tuberculosis.
8. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease [Section 15.2], myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
9. Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

10. History of malignancy within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
11. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia. Severe infection is defined as that requiring inpatient treatment of hospitalization
12. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
    - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
13. Prior allogeneic stem cell or solid organ transplantation
14. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
15. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 6 months after the final dose of atezolizumab
16. Current treatment with anti-viral therapy for HBV. Patient on suppressive therapy should excluded.
17. Treatment with investigational therapy within 28 days prior to initiation of study treatment
18. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
19. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
20. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    - Patients who received acute, low-dose (defined as < 200 mg / day hydrocortisone or equivalent) corticosteroid treatment (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study after Principal Investigator confirmation has been obtained.
    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
21. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
22. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
23. Concurrent identifiable primary cutaneous head and neck squamous cell carcinoma tumor.
24. Pregnant or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment

4.3 Inclusion of Women, Minorities, and Other Underrepresented Populations

Recruitment is open to all minorities and both genders. Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the respective target population.

5. STUDY EVALUATIONS

5.1 Study Assessments

The schedule of activities to be performed during the study is provided in section 6. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

5.1.1 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

5.1.2 Physical Examinations

A complete head and neck physical examination will be performed at screening and other specified visits as per the discretion of the study physician. Any abnormality identified at baseline should be recorded in the patient's medical records.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events in the patient's medical records.

5.1.3 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature.

Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Table 1).

Table 1 Timing for Vital Sign Measurements for First and Subsequent Infusions

Drug	Timing for Vital Sign Measurements	
	First Infusion	Subsequent Infusions
Atezolizumab	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated.	• Within 60 minutes prior to the atezolizumab infusion • Record patient's vital signs during or after the infusion if clinically indicated

5.1.4 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 2 weeks following treatment initiation up to the date of surgery. After surgery they will be assessed at 1 week and 1 month postoperatively, and no longer an interval than every 3 months thereafter, regardless of dose delays, until radiographic disease recurrence/progression per iRECIST or two years have passed since completion of adjuvant treatment. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include contrasted CT or MRI scans of the head and neck as well as a PET CT. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed. At the investigator's discretion, other methods of assessment of measurable disease as per iRECIST may be used.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments.

Overall response at a single timepoint will be assessed by the investigator using iRECIST (see Section 15.9) after the two neoadjuvant doses. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

5.1.5 Laboratory, Biomarker, and Other Biological Samples

Pregnancy testing every three weeks should be performed for medicinal products that have demonstrated or suspected teratogenicity and/or genotoxicity, defined as meeting either of the following criteria:

- Insufficient or unavailable nonclinical data
- Demonstrated or suspected human teratogenicity/fetotoxicity in early pregnancy: a malformative effect has been demonstrated in humans or is suspected on the basis of class effects, the protocol-mandated study treatment has genotoxic potential, or nonclinical data indicate a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy

Additional pregnancy testing may also be warranted, taking into account the duration of the study.

Samples for the laboratory tests will be sent to the study site's local laboratory for analysis:

The following laboratory tests performed at screening only:

- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA
    - If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA
    - If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
- Coagulation: INR, and aPTT

The following laboratory tests will be performed at screening and each follow-up visit (unless specified otherwise):

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH
- Pregnancy test
    - All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Thyroid function testing at screening, neoadjuvant cycle 2, and every other adjuvant cycle (i.e., adjuvant cycles 1, 3, 5, etc.)
    - Testing includes thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- Serum amylase and lipase testing at screening, neoadjuvant cycle 2, and every other adjuvant cycle (i.e., adjuvant cycles 1, 3, 5, etc.)

The following samples may be sent to one or several central laboratories or to the Investigator or a designee for analysis as indicated clinically:

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti-double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Blood and serum samples for exploratory research on biomarkers

- Archival or newly collected tumor tissue sample obtained at baseline and/or at surgery for determination of *PD-L1 expression* and for exploratory research on biomarkers

  Although any available tumor tissue sample can be submitted, we will preferentially try to secure a representative FFPE tumor specimen in a paraffin block, fresh frozen tumor specimen or at least 10 slides containing unstained, freshly cut, serial sections should be submitted along with an associated pathology report prior to study enrollment.

  Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred. However, all specimen types (e.g., fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples) are acceptable. Tumor tissue from bone metastases that have been decalcified is not advisable.

  If archival tumor tissue is unavailable or is determined to be unsuitable for exploratory research, a pretreatment tumor biopsy is required.
- Tumor tissue sample obtained at time of initial enrollment, during surgery and any persistent/recurrent disease after definitive treatment, if deemed clinically feasible, for exploratory research on biomarkers

  Biopsies at the time of recurrence/progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to: analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, circulating tumor DNA, or RNA, or exosomes, analysis of mutations, and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Research will aim to distinguish germline mutations from somatic mutations. NGS methods may include whole exome sequencing (WES) or whole genome sequencing (WGS).

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research, biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Blood samples collected for WGS or WES will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Blood, plasma, serum, tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

5.2 Assessment of Safety

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is

immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions (See Table 2). Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Section 7.4. Refer to Section 9 for details on safety reporting (e.g., adverse events, pregnancies) during the study.

5.2.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, pericarditis, pericardial effusion, cardiac tamponade, myocarditis, pericardial disorders, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.2.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- Death
- Loss to follow up

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient’s medical records. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

5.3 Treatment and Patient Discontinuation

Patients must permanently discontinue study treatment (atezolizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient’s potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient’s safety if he or she continues study treatment
- Investigator discretion
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). In the adjuvant setting, any documented recurrence of tumor will be considered a treatment failure qualifying the patient for discontinuation of the study

The primary reason for study treatment discontinuation should be documented in the patient's medical records. Patient who discontinue treatment will be proceed with SoC treatment. In the neo-adjuvant setting, patient will proceed to definitive surgery with or without adjuvant therapy. In the adjuvant setting, patients will complete their adjuvant course of adjuvant radiation or chemoradiation or continue with routine surveillance. Patients who discontinue study treatment prematurely will be replaced.

6. STUDY CALENDAR

Neoadjuvant Calendar:

Evaluation	Initial Screen[4] ≤28d prior to 1st cycle	Patient Enrolled (0 Day)	Week 1 Neoadjuvant cycle 1 (±3d)	Week 4 Neoadjuvant cycle 2 (±3d)	Week 6 Post-neo-adjuvant: Imaging & Safety (±10d)	Surgery[1]
Inclusion/Exclusion Criteria	X					
Demographics	X					
Medical History	X					
Weight and Vital Signs	X		X	X	X	
Atezolizumab			X	X		
MRI or CT Head and Neck	X				X	
PET	X					
Blood Collection[5]	X		X	X	X	X
Tissue Collection[5]	X					X
Physical Exam	X		X	X	X	
Urinalysis	X					
Pregnancy Test	X					
Adverse Events			X	X		X

Adjuvant Calendar: Patient with pCR at time of surgery

Evaluation	Post-surgery Visit 1 week (±3d)	Post-surgery Visit 1 month (±14d)	Surveillance Follow Up Every 3 mo to 3 years (±14d)
Inclusion/Exclusion Criteria			
Demographics			
Medical History			
Weight and Vital Signs	X	X	X
Atezolizumab			
MRI or CT Head and Neck			
PET			X[2]
Blood Collection[5]			X
Tissue Collection[5]			
Physical Exam	X	X	X
Pregnancy Test			
Adverse Events	X	X	

Adjuvant Calendar: Patient with residual disease at time of surgery

Evaluation	Post-surgery Visit 1 week (±3d)	Post-surgery Visit 1 month (±14d)	Adjuvant Cycle #1[6] < 7 wks post-op			Adjuvant Cycle #2 +3W (±3d)			Adjuvant Cycles #3 - #15 +3W (±3d)	Surveillance Follow Up Every 3 mo to 3 yr [3] (±14d)
			Weeks							
			1	2	3	4	5	6		
Inclusion/Exclusion Criteria										
Demographics										
Medical History										
Weight and Vital Signs	X	X	X			X			X	X
Atezolizumab			X			X			X	
MRI or CT Head and Neck										
PET										X[2]
Blood Collection[5]			X			X			X	X
Tissue Collection[5]										
Physical Exam	X	X	X			X			X	X
Urinalysis										
Pregnancy Test			X			X			X	
Adverse Events	X	X	X			X			X	X[7]
Atezolizumab 1200 MG			X			X			X	
Adjuvant Radiation			X	X	X	X	X	X		

1. Surgery must be completed within 10 weeks after patient is enrolled.
2. Only performed at 3mo follow up visit per standard of care.
3. If the patient is unable to attend the standard of care office appointment they will be contacted via video or phone visit.
4. Any screening assessments performed within 28 days prior to the consent signing can be accepted.
5. See section 5.1.5.
6. Start adjuvant therapy more than 4 weeks after and within 7 weeks after surgery per SOC.
7. AE monitoring at first surveillance visit only ≥ 30 days following last dose of Atezolizumab

7. DRUG INFORMATION – ATEZOLIZUMAB

7.1 Description

Atezolizumab (Tecentriq) is an anti-PD-L1 monoclonal antibody developed by Genentech. It is an immunotherapeutic that blocks the PD-1: PD-L1 axis between host immune cells and tumor cells, allowing for immune recognition and activation against cancer.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Section 15.9. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

7.2 Formulation, Packaging, and Handling

The investigational product will be provided by Genentech. Atezolizumab should be prepared in accordance with the package insert and local master formulas.

The atezolizumab 1200 mg drug product will be supplied in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution of 60 mg/mL intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

For information on the formulation and handling of atezolizumab, see the Atezolizumab Investigator's Brochure.

7.3 Administration

Table 2. 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.

Any overdose or incorrect administration of atezolizumab should be noted in the patient's medical records. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records. Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 7.4.

7.4 Management of Atezolizumab-Specific Adverse Events

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

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-mediated adverse events prior to initiating therapy and throughout treatment and follow-up. There should be a high level of suspicion that new symptoms are treatment related.
- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or appropriate delegate).

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study.

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed

MANAGEMENT GUIDELINES

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 3.

Table 3. Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c, d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.

Event	Management
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the sponsor. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or appropriate delegate). The sponsor may be reached at 916-734-2790 (also see page 1 for the sponsor's contact information).

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 4.

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

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

Table 4. Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:**

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

LFT = liver function test.

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

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

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

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 5.

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

Table 5. Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended.

Event	Management
	• For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 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, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the sponsor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 6.

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.

Table 6 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab and contact the sponsor for life-threatening immune-mediated hypothyroidism. [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.

Event	Management
Grade 2 hyperthyroidism	• Consider withholding atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to an endocrinologist. • Resume atezolizumab when symptoms are controlled, and thyroid function is improving. • Permanently discontinue atezolizumab for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. 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. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control.

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 7.

Table 7 Management Guidelines for Ocular Events

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

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

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 8.

IMMUNE-MEDIATED MYOCARDITIS

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 8.

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 (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 Table 8. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly. Atezolizumab should be permanently withdrawn for any grade confirmed immune-mediated pericardial disorders.

Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a pericardial disorder on prior treatment with other immune-stimulatory anticancer agents.

Table 8 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and contact the sponsor. • 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.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in Table 9.

If a patient develops suspected cytokine-release syndrome 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.

Table 9 Management Guidelines for Infusion-Related Reactions Cytokine-Release Syndrome

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

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

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

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

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

a. Grading system for these management guidelines is based on ASTCT Consensus Grading Scale for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

b. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and who 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, antipyretic medications, analgesics,

bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

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

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

For subsequent infusions, administer oral premedication with antihistamines, antipyretics medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

f. Refer to Riegler et al. (2019)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 10.

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

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

GI = gastrointestinal.

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

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash reported with the use of atezolizumab were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 11.

Table 11 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.

Event	Management
	• If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact the sponsor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

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

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Additionally, immune-mediated myelitis and immune-mediated facial paresis have been associated with the use of PD1/PD-L1 immune checkpoint inhibitors as a class of medications. 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 are provided in Table 12.

Table 12 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy,	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy:

Event	Management
including facial paresis, Grade 2	– If event resolves to Grade 1 or better, resume atezolizumab. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor. [c] • For facial paresis: – If event resolves fully, resume atezolizumab [b] – If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the sponsor. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the sponsor. [c] • Refer patient to neurologist • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the sponsor. [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.
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab and contact the sponsor. • 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 and contact the sponsor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

[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 assessment of benefit-risk by the investigator and in alignment with the protocol requirement for 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 must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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.

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 13.

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact the sponsor. • 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.

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Renal Events

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

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

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

IMMUNE-MEDIATED MYOSITIS

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 15.

Table 15 Management Guidelines for Immune-Mediated Myositis

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

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

[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 assessment of benefit-risk by the investigator and in alignment with the protocol requirement for 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 must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator.

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).

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

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/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 Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

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

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 16.

Table 16 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

7.5 Instructions for Initiation of Each Cycle

To initiate treatment for Cycle 1 start, the following criteria must be met:

- WBC ≤ 25,000/mm^3 (leukapheresis and hydroxyurea are allowed to meet this criteria)
- Total bilirubin ≤ 3x ULN
- Serum creatinine ≤ 1.5x ULN
- The ANC is ≥ 1000/mm^3;
- The platelet count is ≥ 50,000/mm^3;
- Any grade II-IV drug-related non-hematological adverse effect that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to grade ≤ 2 severity;
- No evidence of life-threatening infection.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

7.6 Ordering / How Supplied

Atezolizumab is investigational in this protocol and will be supplied by Genentech at no cost for use in this protocol.

7.7 Disposal and Destruction

Drug supply will be disposed of according to institutional standard operating procedures and policies. Accurate records of all investigational product received at and dispensed from the study site should be recorded on the drug accountability record.

7.8 Concomitant Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such therapies recorded in the patient's medical records.

7.6.1 Permitted Therapy

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

- Oral contraceptives
- 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

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms

may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and B_2-adrenergic agonists; see Section 15.9. Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

7.8.1 Cautionary Therapy for Atezolizumab-Treated Patients

7.8.1.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section 15.9).

7.8.1.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown.

7.8.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer, with the exception of the standard of care course with surgery followed by adjuvant radiation as outlined (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.2, and during study treatment, until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 30 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five drug elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab. Corticosteroids are permitted per section 7.4 for management of irAEs.

8. TREATMENT COMPLIANCE

The investigators and clinical trial coordinators will ensure appropriate patient treatment compliance according to the proposed treatment and surveillance timelines.

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

Patients who wish to stop taking the study medication will have the opportunity to remain in the study for long-term follow-up. The study will continue to monitor these patients for safety and oncologic treatment.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival status after the Final Visit.

Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the IRB The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to institutional, federal and any other appropriate committees and/or sponsors.

9. SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern.

9.1 Adverse Event Definition

Any patient enrolled in the trial who signed the consent form and received at least one dose of atezolizumab will be eligible for adverse event reporting. Only laboratory abnormalities that result in signs or symptoms that require intervention or follow up and are considered clinically significant should be recorded as AEs. All other AEs whether serious or non-serious will be entered into the institutional database from the time of first protocol intervention up until 30 days after the last dose of study drugs. The Principal Investigator or designee will be responsible for assigning attribution to the study treatment.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified

  AE reporting period, including signs or symptoms associated with

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

investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

9.1.1 Causality (Attribution) of Adverse Events

The investigator is to assess the causal relation of all AEs (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related: Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Unlikely: The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Probably Related: The AE is likely related to investigational product.

Definitely Related: The AE is clearly related to use of the investigational product.

9.2 Serious Adverse Events

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening (Note: the term “life-threatening” refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction. It does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person’s ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

9.3 Adverse Event Documentation

All AEs must be recorded on case report forms (CRFs). Documentation must be supported by an entry in the subject’s file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

9.3.1 Adverse Events of Special Interest

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

The following AEs are considered of special interest and must be reported to the Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3 \times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
    - Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3 \times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Data related to a 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.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, macrophage activating syndrome, hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

9.4 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

9.4.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported beginning at initiation of study treatment until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to atezolizumab (see following guidance), and actions taken.

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

Yes

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

No

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

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I. or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

9.5 Procedures for Eliciting, Recording, and Reporting Adverse Events

9.5.1 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.5.2 Specific Instructions for Recording Adverse Events

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

9.5.2.1 Diagnosis versus Signs and Symptoms

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

9.5.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

9.5.2.3 Preexisting Medical Conditions

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

9.5.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

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

9.5.2.5 Pregnancies

If a female subject becomes pregnant while receiving atezolizumab or within 5 months after the last dose of atezolizumab, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported to Genentech as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the atezolizumab should be reported to Genentech, Inc. as an SAE.

9.5.2.6 Post-Study Adverse Events

After the end of the adverse event reporting period (defined as 30 days after the last dose of study drug), the investigator should report all deaths (regardless of cause) and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study that is believed to be related to prior exposure to study drug.

Case Transmission Verification (CTV) will be performed by both parties during this period to ensure successful transmission of Single case reports.

9.5.2.7 Reconciliation (Case Transmission Verification)

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

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

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

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

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

9.6 Serious Adverse Event Reporting

UC Davis will be responsible for collecting all protocol-defined Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all the above mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints ***with*** an AE should be sent to:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All Product Complaints ***without*** an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	*15 calendar days of the awareness date*
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

It is understood and agreed that the Sponsor will be responsible for the evaluation of SAEs, AESIs, Special Situation reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligation are met.

Serious adverse events (SAEs), AEs of special interest (AESIs), pregnancy reports, and, other Special Situation Reports and Product Complaints (with or without an AE) where the patient has been exposed to the Product, will be sent on a MedWatch, CIOMS I form, or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- SADRs (Serious Adverse Drug Reaction):
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.
- Other SAEs
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.
- AESIs
  AESIs requiring expedited reporting shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.
  Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Special Situation Reports
  The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:
  - Data related to the Product usage during breastfeeding
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

  In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

  - **Special Situation Reports**, as defined above, shall be transmitted to Roche within thirty (30) calendar days of the awareness date.

Pregnancy reports

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

9.6.1 Reporting Requirements for Adverse Events Originating from Patient Reported Outcomes

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event and Special Situation Reporting Form or MedWatch form.

9.6.2 Additional Reporting Requirements for IND Holders

For Investigator Sponsored IND Studies there are some additional reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 312.32.

Sponsor-investigators of studies conducted under an IND are required to report all serious, unexpected, and related adverse events directly to the FDA on a MedWatch Form FDA 3500A within 7 (if fatal or life-threatening) or 15 calendar days of first awareness, as described below.

Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

The Sponsor-Investigator will notify the FDA according to the following timelines:

- within **7 calendar days** of any unexpected fatal or life-threatening adverse event with possible relationship to study drug;
- within **15 calendar days** of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the

event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

Email: usds_aereporting-d@gene.com

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

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report to the FDA. For adverse events that are either serious but do not meet the criteria for expedited reporting or are not serious, the FDA will be notified at the time of the IND Annual Report.

9.6.2.1 MedWatch 3500A Reporting Guidelines

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

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

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

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

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

9.6.3 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The Investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

The Investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Genentech will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

9.6.4 Queries

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

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

9.6.5 Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that the Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If the sponsor issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist the sponsor with signal and risk management activities related to the Product within the Study.

Genentech will also provide the sponsor with any new relevant information that may modify, or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

9.6.6 Compliance with Pharmacovigilance Agreement / Audit

The sponsor and Genentech shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then

discuss and agree in good faith upon the audit scope, agenda, and execution of the audit. The requesting Party will bear the cost of the audit.

9.6.7 Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Office of Clinical Research (OCR) policies. The UC Davis IRB can be reached at (916) 703-9151.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design and Overview of Primary and Secondary Endpoints

This is a Phase II single-arm trial investigating the efficacy of the anti-PD-L1 antibody atezolizumab (Genentech) in the neoadjuvant setting for patients with regionally metastatic cutaneous head and neck squamous cell carcinoma with a historic or unknown primary. This will be an open-label trial reporting response rates with pCR as the primary endpoint.

Due to the nature of single arm and small sample size, we will not adjust our analyses for multiplicity, but we will present all outcomes we studied in the single paper with pre-specified designation of each outcome (e.g., primary or secondary/exploratory). Also, formal hypothesis testing will be avoided or properly accompanied/indicated by warning (e.g., a historical control for comparator or other comparability issues).

We will summarize continuous data at baseline with standard descriptive statistics, e.g., mean and SD (or median and IQR) and binary data with frequency and proportion. For continuous and binary outcomes data, point estimates and 95% CIs will be computed for appropriate parameter estimable (e.g., mean or median with accounting for censoring, if needed) and the Clopper and Pearson exact binomial method (with no censoring), respectively.

Primary Endpoints

Pathologic Complete Response (pCR)

pCR is defined as having no residual invasive squamous cell carcinoma within the primary tumor and all resected lymph nodes as assessed by the pathologist at the time of primary resection. The rate of pCR is defined as the proportion of patients demonstrating pCR.

Major Pathologic Response (mPR)

mPR is defined as having ≤ 10% residual invasive squamous cell carcinoma within the primary tumor and all resected lymph nodes as assessed by the pathologist at the time of primary resection. The rate of mPR is defined as the proportion of patients demonstrating mPR.

Event Free Survival (EFS)

EFS is defined as the time from randomization to the first day of the any of the following events:

- Radiographic evidence of recurrence or disease progression per iRECIST
- Clinical evidence of recurrence or disease progression as assessed by clinical exam and confirmed by biopsy.
- Death due to any cause

A non-parametric Kaplan-Meier (KM) method will be used to estimate the 2-year EFS curve. Participants who do not experience recurrence or disease progression at the time of their last

follow-up will be censored. Recurrence, all-cause death and disease-specific death will be likewise examined using the KM method to determine estimates of 2-yr disease-free survival, overall survival and disease-specific survival. Because we will use historical control (not concurrent control or parallel trial, despite the availability of raw data), we will try to focus on a description of results and 95% CI, instead of statistical significance.

Longitudinal data will be summarized similarly and accompanied by time points to illustrate possible trends. When we utilize historical controls (for description and informal comparison), we will use a control sample matched on key confounders (e.g., age, gender, key comorbidities and medical histories). We expect approximately 40 control patients, thus, achieving approximately 1:2 ratio in sample size for current sample: comparator.

Secondary Endpoints

FDG avidity of nodal disease sites as measured by PET

FDG avidity of nodal sites will be quantified according to standardized uptake value (SUV). The SUV is the ratio of the image derived radioactivity concentration of the lesion of interest and the whole body concentration of the injected radioactivity. SoC staging PET/CT will be performed prior to initiation of treatment and as a post-treatment scan 3 months after completion.

The association of the SUV of the regionally metastatic focus of disease to the pathologic response to neoadjuvant therapy at the time of surgery will be examined. A t-test (or nonparametric counterpart) and multiple regression will be used to compare mean SUV between patients who experience cPR to the mean SUV of those with residual disease after neoadjuvant therapy, where the latter will adjust patient characteristics and potential confounders. In addition, the mean SUV of additional sites of regionally metastatic disease will be studied.

Overall Response Rate by iRECIST

See Section 15.7.

Plasma exosome levels

Blood plasma collection for research investigation into tumor-associated exosome levels will be coordinated at the time of lab blood collection during the study as per the timeline. A purple-top tube will be collected at transferred to our research laboratories for isolation and analysis of exosomes. The collection points may include initial screen, neoadjuvant doses 1 and 2, post-neoadjuvant safety, surgery, and during adjuvant treatment. For each sample, we will analyze exosome total protein content, density, and size distribution. We will additionally utilize flow cytometry and multiplexed microarrays to investigate biomarker levels on tumor-associated exosomes (e.g., EGFR, CD44). We will investigate the use of novel Raman spectroscopy techniques with our collaborators at UC Davis to further enhance our analysis for tumor-associated exosomes.

Toxicity (adverse events) determined by CTCAE v5

See Section 15.6.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Descriptive statistics will be provided for adverse events.

The analysis of safety results will follow a tiered approach. Adverse events (specific terms as well as system organ class terms) are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

There are no Tier 1 events for this protocol as acceptable and manageable safety/tolerability profile of atezolizumab monotherapy has been established.

Tier 2 Events

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit a specific AE; all other AEs will belong to Tier 3. In addition, specific Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and specific SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, any drug related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, discontinued due to an AE, and death that are not pre-specified as Tier 1 endpoints will be classified as belong to “Tier 3”. Laboratory test toxicity grade shift from baseline is considered Tier 3 event.

10.2 Sample Size Estimation / Evaluation of Efficacy / Accrual Rate

A Simon’s two-stage design is used to calculate an optimal sample size and minimal efficacy threshold using a primary end-point of pCR. We assume an alpha type I error of 0.05 and power of 80% and set our response probability for an ineffective drug (p_0) at pCR < 0.05 and our response probability of an effective drug (p_1) at pCR > 0.30.

Sample Size

Given these parameters, a total of 18 subjects (n) with 3 or more responses would support continued investigation of the proposed treatment paradigm.

Evaluation of Efficacy

In stage 1 of our study, 5 (n_1) patient will be enrolled and if no responses are observed, the trial will be stopped early for futility.

Accrual Rate

We estimate an accrual of 1-2 patients per month, with a goal accrual of 18 patients in this trial

10.3 Evaluation of Safety

Safety and tolerability will be assessed through detailed history and physical at each clinical visit and documented using CTCAE v5. In addition, patients will complete EORTC QLQ-C30 and EORTC QLQ-H&N35 surveys at each clinic visit.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

11.3 Study Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Office of Clinical Research (OCR) policy. To register a patient, the data manager or designee must complete the Eligibility Checklist and the Patient Registration Form. After verifying the eligibility, the OCR coordinator will register the patient onto the study and assign a patient accession. Administration of study drug may not be initiated until the patient is registered (See section 15.3, Registration Guidelines).

11.4 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

11.5 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD OCR. Medical records of patients will be maintained in strict confidence according to legal requirements. The investigator will grant monitor(s) and auditor(s) from Genentech or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained

and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.6 Protocol Compliance and Deviations

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies. Any departures from the protocol must be fully documented in the source documents.

11.7 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Genentech, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Genentech by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to patients
2. Failure to enter patients at an acceptable rate
3. Insufficient adherence to protocol requirements
4. Insufficient complete and/or evaluable data
5. Plans to modify, suspend, or discontinue the development of the drug

11.8 Aggregate Reports

11.8.1 IND Annual Reports

Not applicable, as the study is IND exempt.

11.8.2 Other Reports

The Investigator will forward a copy of the Publication to Genentech within one year after last study visit.

11.9 Study Close-Out

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

Atezolizumab IIS Clinical Operations: anti-pdl-1-mpd3280a-gsur@gene.com

And to Genentech Patient Safety CTV oversight mailbox at: ctvistsa@gene.com

11.10 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

11.11 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan. Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

11.12 Data and Safety Monitoring

In addition to the requirements for adverse event reporting, this protocol is also subject to the UC Davis Comprehensive Cancer Center's (UCDCCC) Data and Safety Monitoring Plan. The UCDCCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCCC to fulfill its mission in conducting high quality clinical cancer research.

As per UCDCCC Office of Clinical Research (OCR) standard operating procedures, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events, and to determine if dose escalation is warranted, when applicable.

According to the UCDCCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed at least every 3 months by the UCDCCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary. For study specific data safety monitoring: see section 12 for management, quality assurance, storage, and access to data; see section 9 for adverse event collection and reporting; and see section 11.7 for trial termination rules.

The UCDCCC Scientific Review Committee (SRC) determines if a UCDCCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, and adverse event information to ensure subject safety and compliance with protocol defined guidelines.

12. INVESTIGATOR REQUIREMENTS

12.1 Retention of Records

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

12.2 Study Medical Monitoring Requirements

This clinical research study will be monitored both internally by the PI and externally by the UC Davis Health IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the UC Davis Health IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

12.3 Study Medication Accountability

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

12.4 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the UC Davis Health IRB.

13. ETHICAL CONSIDERATIONS

13.1 Compliance with Laws and Regulations

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive MPDL3280A treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 5.3.

13.2 Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

13.3 Institutional Review Board or Ethics Committee

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

13.4 Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

14. REFERENCES

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15. APPENDICES

15.1 ECOG and Karnofsky Performance Status Scores[1,2]

http://ecog-acrin.org/resources/ecog-performance-status

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—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—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare 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 personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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2. Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. Journal of Chronic Diseases; 1960:11:7-33.

15.2 New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

15.3 Study Registration

A. Registrations for this protocol must be made through the Office of Clinical Research (OCR) of the University of California, Davis Cancer Center between normal business hours (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UCD institutions must be on file prior to registration of patients at these institutions.

B. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

C. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Protocol Coordinator must be notified by fax (916-734-4177) 24 hrs prior to proposed treatment start date that the site has a patient to register.

D. Patients may be registered up to 72 hrs prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed to the University of California, Davis Cancer Center Office of Clinical Research in order to register the patient. The UC Davis Protocol Coordinator will review these documents and fax a registration confirmation within 3 hours.
NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

E. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, please contact the PI or Study Coordinator.

15.4 Data Collection Forms

All data will be collected using UC Davis data collection forms. Any and all source documentation shall be maintained.

15.5 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 238-6067

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

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

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

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

15.6 Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

15.7 Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009 and Wolchok et al. 2009) have been developed to allow for unconventional response and progression patterns. These include modified RECIST v1.1 for immune-based therapeutics (iRECIST; Seymour et al. 2017), which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy field could apply to clinical trials.

Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply.

Criteria for determining overall response at a single timepoint per iRECIST are also summarized below.

iRECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions, as described in Section 3.1.

EVALUATION OF LESIONS TO SUPPORT IRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST V1.1

iRECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. RECIST v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in section 15.7. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

TARGET LESIONS

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

NON-TARGET LESIONS

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" relative to baseline (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non–lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the

short axis [see note below]). All new lesions (measurable or non–measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non–measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$ 10 mm and $<$ 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is $<$ 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is $\geq$ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to $<$ 15 mm (or even $<$ 10 mm).

Table 17. Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	• Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	• Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	• New lesions should be evaluated for measurability per RECIST v1.1. • All new lesions (measurable or non–measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints. • Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. • All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

CR = complete response; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.

SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Timepoint response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in a publication by Seymour et al. (2017).

15.8 Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myelitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

15.9 Infusion Reaction and Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

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