ML42362: NEOADJUVANT ATEZOLIZUMAB IN SURGICALLY RESECTABLE ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

Document History	**Notes**
Version 3 Date: 14 Sep 2020	Initial Approval from Genentech
Version 4 Date: 29 Oct 2020	Revision includes: • Addition of information in regulatory considerations regarding the study drug, i.e. reasons why it is IND-exempt • Formatting changes
Version 5 Date: 30 Oct 2020	Revision includes: • Formatting changes, updating ToC • Correcting spelling and grammatical errors
Version 6 Date: 30 Oct 2020	Revision includes: • Formatting changes • Clarification of the primary objective in the statistical plan
Version 7 Date: 04 Nov 2020	Revision includes: • Modified data safety and monitoring plan, including adding a stopping rule • Updated the statistical plan
Version 8 Date: 12 Nov 2020	Revision includes: • Updated the statistical plan including expanding on outcome measures (primary and secondary)
Version 9 Date: 05 Mar 2021	Revision includes: • Updated the AE reporting timeline to Genentech from 15 calendar days to 30 days and clarified site responsibilities for signal management/ risk management for per feedback from Genentech

Version 10 Date: 06 Jul 2021	Revision includes:
	• Formatting and topological changes
	• Added Sumaira Aasi as Co-Investigator
	• Updated Section 4.2
	  o Clarified sources for Medical History
	• Updated Section 4.4
	  o Clarified vital sign data collection
	• Updated Section 4.5
	  o Clarified Screening Scan
	• Updated Section 5.3

Document History	Notes
	○ Clarified study drug storage and dispensation. • Updated Section 7.2 ○ The number of allotted active patients has been increased from three to six based on contemporary subject safety data. • Updated Section 7.3.1 ○ Clarified AE collection • Clarified Procedures in Section 9 ○ Clarified pre-infusion vital sign collection window, screening TSH, and RECIST.
Version 11 Date: 16 Mar 2022	Revision includes: • Clarify language ○ Section 12.3 language has been consolidated with section 7.2 to reflect previous amendment to six patients. • Minor formatting and administrative changes • Update Section 9 Study Calendar ○ Footnote J: Screening lab window extended to 28 days to match Inclusion criteria #7 ○ Screening window clarified to within 28 days prior to start of treatment • Personnel changes ○ Remove Nikita Bedi as study coordinator ○ Add Luis Martinez Ramirez study coordinator
Version 12 Date: 16 MAY 2022	Revision includes: • Clarify language ○ Section 4.5 language to clarify collection of tumor response evaluations ○ Section 9 Study Calendar footnote P & S to clarify collection of RECIST measurements

Document History	Notes

Version 13 Date: 06 DEC 2022	Revision includes:
	• Minor formatting changes
	• Updated Section 3
	  ○ Clarified section by removing limit of 25 patients that can be screened for study as this was an arbitrary number.
	• Updated Appendix I
	  ○ Added management guidelines for
	  ▪ Immune-mediated Myelitis
	  ▪ Immune-mediated facial paresis
	  ○ Updated management guidelines for
	  ▪ Table 1: Pulmonary Events
	  ▪ Table 4: Endocrine Events
	  ▪ Table 6: Immune-related myocarditis
	  ▪ Table 7: Infusion-related Reactions and Cytokine-release Syndrome
	  ▪ Table 9: Dermatologic Events
	  ▪ Table 10: Neurologic Disorders
	  ▪ Table 12: Renal Events
	  ▪ Table 13: Immune-mediated Myositis
	  ▪ Table 14: Suspected Hemophagocytic Lymphohistiocytosis or Macrophage activation Syndrome
	  ○ Updated Infusion related reactions subsection to "Infusion-related Reactions And Cytokine-Release Syndrome" and added updated information
	  ○ Updated Dermatologic events subsection with updated information

Document History	Notes
	○ Updated Lymphohistiocytosis and macrophage activation syndrome subsection with updated information ○ Added new references
Version 14 Date: 29 AUG 2023	Revisions include: • Minor formatting edits • Administrative edits • Updated Appendix G ○ Added autoimmune myelitis to list of autoimmune disease that would exclude a patient from trial. • Updated Appendix I ○ Added missing table header for Table 11: Management Guidelines for Immune-Mediated Myelitis ○ Revised management guideline table numbering for ▪ Table 12: Immune-Mediated Meningoencephalitis ▪ Table 13: Renal Events ▪ Table 14: Immune-Mediated Myositis ○ Updated management guidelines tables with information from IBv19 and associated addendum: ▪ Tables 1-15 ○ Updated references
Version 15 12AUG2024	Revision includes: • Updated Section 1.2 ○ Updated secondary objective to clarify that changes in surgery will be measured by intensity of surgery performed and cost of care.

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Version #15 / Version Date: (12-AUG-2024)

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

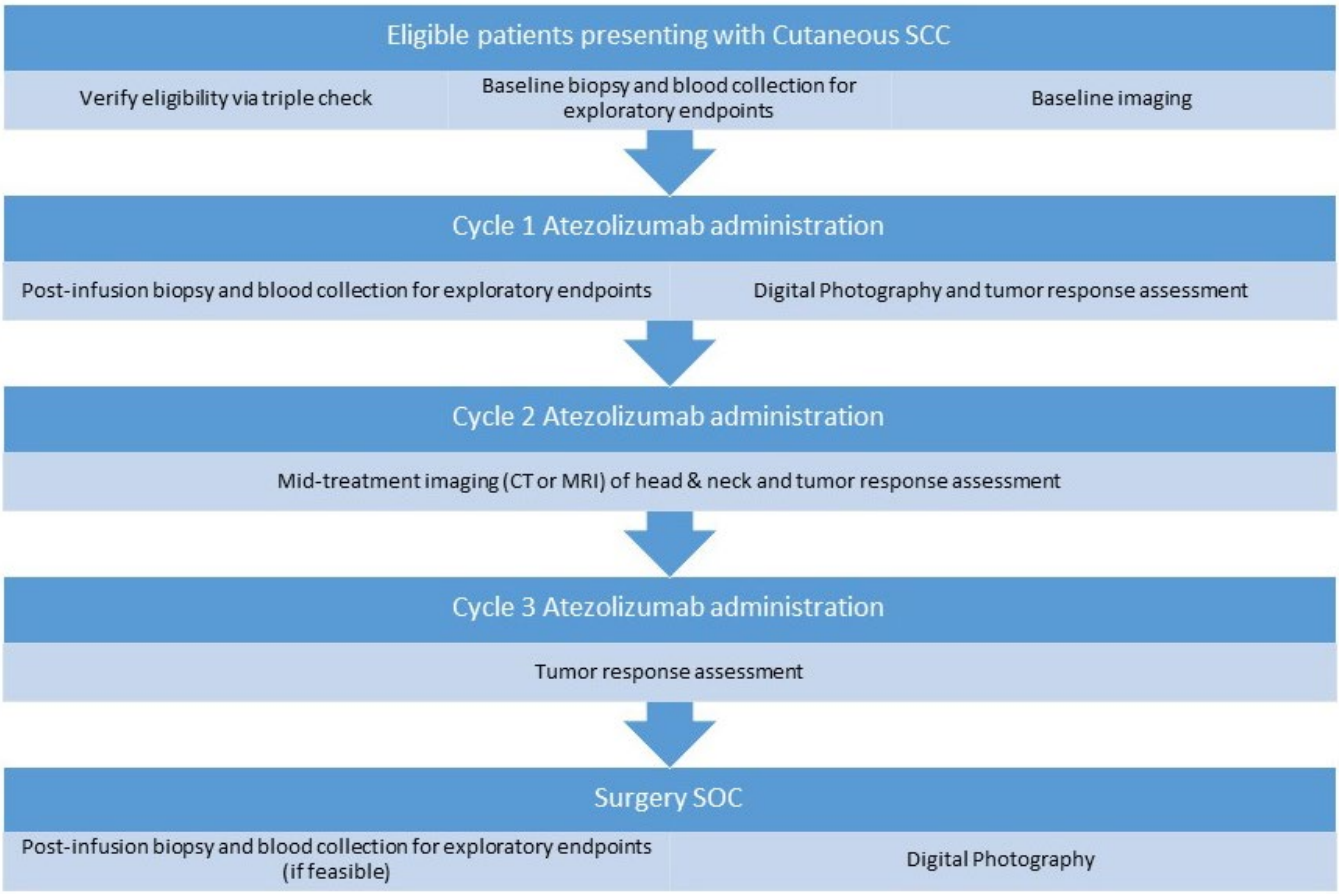
TITLE	Neoadjuvant Atezolizumab in Surgically Resectable Advanced Cutaneous Squamous Cell Carcinoma
STUDY PHASE	N/A Feasibility study
INDICATION	Cutaneous Squamous Cell Carcinoma
INVESTIGATIONAL PRODUCT OR PROCEDURE	Atezolizumab (RO5541267)
PRIMARY OBJECTIVE	• Determine the feasibility of three doses of atezolizumab prior to surgery in patients with advanced cutaneous squamous cell carcinoma

SECONDARY OBJECTIVES	• Assess response rates to neoadjuvant atezolizumab
	  ○ Objective response rate following completion of neoadjuvant therapy based on RECIST 1.1 criteria
	  ○ Pathological response rate (major and complete pathological response) in final surgical resection specimen
	• Assess change in surgical plan, as measured by intensity of surgery performed, cost of care, surgical margins or vital structures preserved, following neoadjuvant treatment
	• Assess safety and tolerability of neoadjuvant atezolizumab

EXPLORATORY OBJECTIVES	• Perform correlative studies to assess pre-treatment biological markers, including PD-L1 expression, that are associated with response to atezolizumab • Evaluate tumors prior to and during treatment to identify neoantigen profile changes and T-cell receptor repertoire changes • Evaluate changes in cell-free DNA, cytokine profiles associated with immune system activation, and lymphocyte subpopulations before and during treatment • Analysis of genes or gene signatures associated with tumor immunobiology
TREATMENT SUMMARY	Subjects will receive neoadjuvant atezolizumab (1200 mg). Atezolizumab will be administered by intravenous (IV) infusion

	at a fixed dose of 1200 mg on Day 1 (+/- 3 days) of each 21-day cycle for a total of 3 doses prior to surgery, unless there is clinical or radiographic evidence of disease progression.
SAMPLE SIZE	20 evaluable patients
STATISTICAL CONSIDERATIONS	See stats section

SCHEMA


Eligible patients presenting with Cutaneous SCC
Verify eligibility via triple check
Baseline biopsy and blood collection for exploratory endpoints
Baseline imaging
Cycle 1 Atezolizumab administration
Post-infusion biopsy and blood collection for exploratory endpoints
Digital Photography and tumor response assessment
Cycle 2 Atezolizumab administration
Mid-treatment imaging (CT or MRI) of head & neck and tumor response assessment
Cycle 3 Atezolizumab administration
Tumor response assessment
Surgery SOC
Post-infusion biopsy and blood collection for exploratory endpoints (if feasible)
Digital Photography

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AJCC	American Joint Committee on Cancer
aPTT	Activated partial thromboplastin time
CR	Complete response
cSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IgG	Immunoglobulin G
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous
LPLV	Last patient, last visit
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PK	Pharmacokinetic
PDL1	Programmed death-ligand 1
RECIST	Response evaluation criteria in solid tumors
ULN	Upper limit of normal
U.S.	United States

1. OBJECTIVES

1.1. Primary Objective

The primary objective is to determine the feasibility of three doses of atezolizumab prior to surgery in patients with advanced cutaneous squamous cell carcinoma. The primary outcome measure for each patient is an indicator for successfully completing 3 cycles of neoadjuvant atezolizumab, followed by surgical resection of remaining disease. The treatment will be evaluated as non-feasible for patients who have disease progression during neoadjuvant treatment, discontinue study medications due to toxicity, or are not able to undergo curative surgical resection after 3 cycles of treatment.

This study will gather safety and efficacy data to design a larger, more definitive trial that assesses important clinical endpoints including whether surgical margins can be reduced without compromising local control, the impact of neoadjuvant treatment on disease recurrence rates, and the role of adjuvant radiation and immunotherapy in high-risk patients. This study will also validate the neoadjuvant approach. If the neoadjuvant approach is feasible, this study may allow for the addition of an additional cohort that evaluates the potential use combination immune checkpoint inhibitors which may have a more potent anti-tumor effect.

1.2. Secondary Objectives

The secondary objectives of the trial include:

- Assess response rates to neoadjuvant atezolizumab
    - Objective response rate following completion of neoadjuvant therapy based on RECIST 1.1 criteria
    - Pathological response rate (major and complete pathological response) in final surgical resection specimen
- Assess change in surgical plan, as measured by intensity of surgery performed, cost of care, surgical margins, or vital structures preserved, following neoadjuvant treatment
- Assess safety and tolerability of neoadjuvant atezolizumab

1.3. Exploratory Objectives

The exploratory objectives of this study are:

- Perform correlative studies to assess pre-treatment biological markers, including PD-L1 expression, that are associated with response to atezolizumab
- Evaluate tumors prior to and during treatment to identify neoantigen profile changes and T-cell receptor repertoire changes
- Evaluate changes in cell-free DNA, cytokine profiles associated with immune system activation, and lymphocyte subpopulations before and during treatment
- Analysis of genes or gene signatures associated with tumor immunobiology

2. BACKGROUND

2.1 Study Disease

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer in the US, with over 700,000 cases diagnosed annually, and the incidence is likely to continue to rise. While most cases are successfully treated with ablation or minor surgical resection, approximately 2-4% of patients can present with large recurrences, deeply invasive local disease, extensive perineural invasion, or regional metastases. In these cases of advanced disease, wide surgical resection, lymph node dissection, and reconstructive surgery are often necessary, and usually followed with adjuvant radiation therapy. Despite this aggressive treatment approach, multiple studies of advanced cSCC in the U.S. have shown recurrence rates that range from 28-42%, and OS rates that range from 22-54%. Accurate estimates of the mortality burden are elusive since cSCC is not captured by national cancer registries, however estimates vary from 2,000 to 15,000 annual deaths in the U.S. (Karla, Ansouri, ASCO)

In addition, since 80% to 90% of these lesions occur in the head and neck, even smaller lesions can leave patients with significant disfigurement and a decreased quality of life. Cosmetically sensitive regions such as the nose, eyelids, and ear are very challenging to reconstruct when >50% of the structure is removed. Functionally sensitive regions such as the orbital region or lower lip can be significantly distorted causing drooling, impaired vision, or corneal exposure. In rare cases, the cancer may require removal of the orbital contents leaving a patient with monocular vision. Multiple studies have shown the significant distress, anxiety, and psychological impact of such outcomes. (Moolenburgh, Radiotis)

This study will consider patients who have clinically advanced disease with increased risk of recurrence, and patients with disease for which surgery would result in significant disfigurement or functional impairment (see Inclusion Criteria).

Inhibition Of Pd-1/Pd-L1 Pathway In Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma most often arises in areas of high sun exposure. cSCC has among the highest tumor mutational burden (45.2 mutations/Mb) due to cumulative ultraviolet light-induced mutations. (Walter) This high mutational burden is believed to lead to increased immunogenicity due to the very high expression of neoantigens. (Martincorena) This makes cSCC, similar to other cutaneous malignancies such as malignant melanoma and Merkel cell carcinoma, a particularly attractive target for immunotherapeutic approaches.

Studies have shown the impact of targeting the PD-1/PD-L1 pathway in cSCC, and found favorable results compared to the relatively low response rates of cytotoxic chemotherapy (cisplatin) and anti-EGFR antibodies, with ORR < 30%. The most significant study was for cemiplimab, which received FDA approval for the treatment of locally advanced or metastatic cSCC in patients who were not eligible for curative surgery or radiation. In this study, cemiplimab, an IgG4 anti-PD-1 monoclonal antibody, was found to have an ORR of 46.7%, with duration of response exceeding 6 months in 61% of patients. (Migden)

Other PD-1/PD-L1 checkpoint inhibitors have shown promising activity in cSCC in small cases series, leading to additional larger trials in the locally advanced and recurrent/metastatic populations. Nivolumab (NCT04204837), pemobrolizumab (NCT03284424, NCT02883556), and avelumab in combination with cetuximab (NCT03944941) are three such inhibitors with further studies underway. Additional studies of cemiplimab (NCT03969004) and pembrolizumab (NCT03833167) are being performed in the adjuvant setting following surgery and radiation therapy for advanced lesions

2.2 Study Agent/Device/Procedure

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 and adjuvant settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of non-small cell lung cancer, small-cell lung cancer and Alveolar Soft Part Sarcoma (ASPS). The PD-L1 inhibitors including atezolizumab have been evaluated in head and neck squamous cell carcinoma and shown to have benefit in early stage trials (Colevas, Segal). Its safety, tolerability, efficacy, and immunogenicity in adults with advanced solid tumors was evaluated in a phase I/II global, multicenter, open-label, first-in-human dose-escalation and expansion study. In two different trials, atezolizumab in combination with NT-I7 (rhIL-7-hyFc) (NCT03901573) and in combination with cobimetinib (NCT03108131) is currently being investigated for advanced refractory tumors including cSCC.

Details concerning atezolizumab's clinical development can be found in the investigator brochure.

For clinicaltrials.gov compliance

This study will NOT require an Investigational New Drug application (IND). It is considered IND exempt.

2.3 Rationale

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).

There are several benefits of a neoadjuvant approach to cSCC. Given the critical location of these lesions and the impact on patients from disfigurement and functional impairment, minimizing tissue resection while not compromising outcomes is an important goal of treatment. Reduction in surgical margins in responders may significantly impact a patient's quality of life and patient reported outcomes.

While the most aggressive cSCCs have been treated with adjuvant chemotherapy, use of immune checkpoint inhibitors may have a distinct advantage for being used in the neoadjuvant setting. Inhibition in the presence of a large tumor mass may theoretically be a more ideal time to prime the system and potentially induce a stronger and broader tumor-specific T-cell response. (O'Donnell) Given the significant recurrence rates and mortality associated with advanced cSCC, future studies could assess if this immune response can increase DFS and may ideally select which patients benefit from further treatment in the adjuvant setting. Neoadjuvant window of opportunity trials also provide a unique opportunity to study biological correlates and markers of response in surgically curable disease.

The experience with neoadjuvant treatment is growing. A study of neoadjuvant nivolumab in untreated, surgically resectable early stage non-small cell lung cancer enrolled 22 patients, of which 20 patients were able to complete the 2 cycles of therapy. (NCT02259621) Among these patients, 45% had a major pathological response, and none of the patients had any treatment-related delays in surgery. 20 of 21 patients were able to undergo complete surgical resection. (Forde)

A pilot study in cSCC was presented at the 44th European Society of Medical Oncology in 2019 using 2 doses of neoadjuvant cemiplimab for patients with Stage 3 and 4 cSCC of the head and neck. (NCT03565783) In this study of 20 patients, the treatment was well tolerated with no grade 3 or 4 AEs. 55% of patients achieved a pathological complete response and 15% of patients achieve a major pathological response (<10% viable tumor). All patients were able to proceed with anticipated curative surgical resection. (Gross)

In addition to this trial, other studies have shown a neoadjuvant approach is feasible with cutaneous malignancies and can result in decreased surgical defects. Blank et. al. examined neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma and found that all of the patients in the neoadjuvant treatment arm were able to undergo the anticipated surgery. Of the 9 patients evaluable in the neoadjuvant arm, 78% achieved a significant pathological response and majority had a decrease in lesion size. In a trial of vismodegib used in a neoadjuvant fashion prior to treatment of high-risk basal cell carcinoma, surgical defect size was reduced by 27% in patients who were able to complete 3 months of treatment with all patients able to complete surgical resection. (Ally)

The risks of this trial, similar to other neoadjuvant trials, include the possibility of disease progression resulting in either a more extensive resection that initially anticipated or loss of opportunity for curative surgery. Encouraging data from a preliminary study (NCT03565783, Gross) showed that the risk of this is likely low and worth the potential opportunity to reduce lesion size. This risk will be minimized by careful monitoring of visible lesions following each cycle, and also includes an additional imaging study after the second dose of atezolizumab to check for radiographic evidence of disease progression.

The toxicity profile for atezolizumab is expected to be similar to its use for other indications. Atezolizumab has been generally well tolerated. Adverse events with potentially immune-related 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.

This trial will enroll patients with advanced cutaneous squamous cell carcinoma. Given the significant rates of recurrence and mortality, in addition to the disfigurement and functional impairment resulting from aggressive treatment, this population is considered appropriate for trials of novel therapeutic candidates. This feasibility study will be the first step towards designing a larger trial that examines surgical margin reduction, disease recurrence rates, and optimal adjuvant therapy strategies. If feasible, this study may also test the feasibility of this strategy for use of different combination regimens in the future.

2.4 Study Design

An overview of the study is provided in the study flowchart (Section 9). Briefly, upon eligibility confirmation and study enrollment, subjects will undergo initial tumor biopsy and receive neoadjuvant atezolizumab (1200 mg). Atezolizumab will be administered by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 (+/- 3 days) of each 21-day cycle for a total of 3 doses prior to surgery, unless there is clinical or radiographic evidence of disease progression. If clinically feasible, an additional biopsy will be performed after the first dose for biological correlative studies. Patients will be seen prior to each cycle to assess response. A formal assessment including imaging of the head and neck will be performed after 2 cycles of treatment. After the third dose, standard of care surgical resection will be performed. AEs will be assessed up to 30 days after surgical resection. Following surgery, adjuvant therapy will be administered per the standard of care, which includes radiation therapy for AJCC Stage 3 and 4 disease.

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

- **Treatment**: protocol designed to evaluate one or more interventions for treating a disease, syndrome or condition
- **Single Group**
- Number of intervention arms: 1
- **Open**: no masking is used
- Not randomized

- State type of primary outcome or outcome that the protocol is designed to evaluate: Feasibility

2.5 Correlative Studies Background

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 from patients and tested for PD-L1 expression by a central laboratory during the screening period. 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. Fresh tumor tissue will also be collected at baseline and after the first cycle of atezolizumab by biopsy, if deemed clinically feasible by the investigator, to enable analysis of tumor tissue biomarkers related to resistance, neoantigen expression and changes with treatment, 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 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.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.
Patients with advanced surgically-resectable cutaneous squamous cell carcinoma will be screened for enrollment in this study to yield 20 evaluable patients

3.1 Inclusion Criteria

Refer to Participant Eligibility Checklist in Appendix A.

3.2 Exclusion Criteria

Refer to Participant Eligibility Checklist in Appendix A.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any

study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Study Timeline

Primary Completion:
The study will reach primary completion 36 months from the time the study opens to accrual.

Study Completion:
The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur 6 months after the last patient is enrolled. In addition, the Investigator may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 42 months.

4. TREATMENT PLAN

Description of the Study

The schedule of activities to be performed during the study is provided in Section 9. 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.

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 (+/- 3 days) of each 21-day cycle), 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).

4.1 Informed Consent Forms and Screening Logs

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for

screening failure, as applicable.

4.2 Medical History, Concomitant Medication, and Demographic Data

Medical history reported via medical records and/or self-reported by the subject, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) 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. 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.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.3 Physical Examinations

A complete physical examination shall be performed at screening and other specified visits. Any abnormality identified at baseline should be recorded in the patient's medical records.

Limited, symptom-directed physical examinations should be performed at specified postbaseline 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. Clinically insignificant labs or other events need not be recorded or reported.

4.4 Vital Signs

Vital signs will be performed as specified in the study calendar (Section 9). Only clinically significant abnormalities (new or worsened) will be recorded as AE's in the patient's medical records.

4.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and according to the schedule specified in the study calendar (section 9). These are clinical observations and judgements used by the investigator and medical team of the patient's clinical status to determine the appropriateness of continuing study intervention. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. All tumor assessments following surgical resection will be per standards of care.

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.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix F) at baseline and Day 38 (± 4 days).

Screening assessments must include CT scans (with IV contrast) or MRI scans of the primary site (if present), regional lymphatics, thorax, and depending on the location of the tumor, may include other relevant anatomy. PET/CT or CT of the thorax are appropriate preoperative workup; however, cannot substitute for either the CT or MRI of the primary site if present, and regional lymphatics. CT of the thorax need not be repeated after baseline unless there is clinical indication. 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 and MRI scans of regional lymphatics and, if applicable, primary site should be performed. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans) as listed in section 9. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for primary tumor assessment is performed in a positron emission tomography (PET)/CT scanner, all efforts should be made so the CT acquisition is consistent with the standards for a full-contrast diagnostic CT scan.

4.6 Laboratory, Biomarker, and other Biological Samples

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

- See study calendar (Section 9) for details about schedule of laboratory studies

The following samples will be sent to the Investigator or a designee for analysis:

- Plasma samples for exploratory assessment cell-free DNA at baseline and after each cycle of therapy (up to 3 cycles).
- Serum samples for assessment of cytokine profiles associated with immune system activation.
- Peripheral blood mononuclear cells (PBMC) will be collected and cryopreserved after each cycle of therapy (up to 3 cycles) and at the time of surgical resection if deemed for possible, for exploratory identification of antigen-specific T cell receptors (TCR).
- Archival or newly collected tumor tissue sample obtained at baseline for exploratory research on biomarkers
    - 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) are acceptable.
    - 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 following the first and subsequent cycles of therapy and at the time of surgical resection, if deemed clinically feasible, for exploratory research on biomarkers
    - 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, peptide-MHC repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, circulating tumor DNA, or RNA, analysis of mutations, genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes, and analysis of proteins. Research will aim to distinguish germline mutations from somatic mutations and understanding mechanisms underlying immune cell recognition of tumor cells that might predict clinical response to therapy. NGS methods may include whole exome sequencing (WES).

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 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).
- Plasma and/or serum samples collected for PK or immunogenicity analysis and cell-free DNA analysis may be needed for additional characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and tumor tissue samples collected for biomarker research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

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.

Data arising from sample analysis, including data on mutations, will be subject to the confidentiality standards described in Section 11.5.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Investigator policy on study data publication.

4.7 General Concomitant Medication and Supportive Care Guidelines

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 medications should be reported to the investigator and recorded in the patient's medical records.

4.7.1 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
- Administration of steroids at high dose as indicated by the surgical team or anesthesia on the day of surgery or during the post-operative care.
- Other prescription or OTC medicines not known or thought to interfere with the metabolism of or MOA of atezolizumab. Broadly, these typically include antihypertensives, lipid lowering agents, antidepressants, thyroid hormone replacement, oral hypoglycemic agents and insulin.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.2 and 4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-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 β_2-adrenergic agonists; see Appendix I).

4.7.2 Cautionary Therapy for Atezolizumab-Treated Patients

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 Appendix I for details). Administration of steroids at high dose may be indicated to reduce swelling by the surgical team or anesthesia on the day of surgery or during the post-operative care.

Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.3) may be used during the study at the discretion of the investigator.

Prohibited Therapy

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority-approved or experimental, is prohibited for the duration of the study. Adjuvant treatment with radiation and or systemic therapies is permitted per standards of care following the surgical resection.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 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.

4.8 Criteria for Removal from Study

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 determines it is in the best interest of the patient
- 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)

The primary reason for study treatment discontinuation should be documented in the patient's medical records.

4.8.1 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
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator

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. Patients who withdraw from the study will not be replaced.

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.

4.8.2 Study Discontinuation

The Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a

potential health hazard to patients
- Patient enrollment is unsatisfactory

4.9 Alternatives

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. Patients will be closely monitored for any adverse reactions or toxicities, and will be seen after each cycle to minimize risks. In addition, the patients will be undergo imaging to assess tumor progression. The alternative to participating in this study will the current standard of upfront surgical resection without neoadjuvant treatment. This will be offered to patients and presented as an option instead of enrolling in the clinical trial.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

The investigational medicinal product (IMP) for this study is atezolizumab.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 (+/- 3 days) of each 21-day cycle for a total of 3 doses prior to surgery, unless there is clinical or radiographic evidence of disease progression.

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 Appendix H. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 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 clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix H.

Any overdose or incorrect administration of atezolizumab should be noted in the patient's medical records and reported according to Section 7.5 (Special Situations Reports). 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 discontinuation for patients who experience adverse events are provided in Appendix I.

5.2 Availability

Genentech will provide atezolizumab.

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 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.

5.3 Agent Ordering

The drug will be delivered by Genentech to the Stanford Investigational Drug Services (IDS).

Per Stanford standard operating procedures, the Stanford IDS will be responsible for storage of atezolizumab and dispensing of the drug after subjects are screened and enrolled to the study.

5.4 Agent 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.

6. DOSE MODIFICATIONS

No dose modification for atezolizumab is allowed.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

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 (see Section 7.1).

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. Guidelines for managing patients who experience anticipated adverse events, including criteria for treatment discontinuation, are provided in Appendix I. Refer to Sections 7.2-7.6 for details on safety reporting (e.g., adverse events, pregnancies) during the study.

7.1 Potential Adverse Events

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

to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

7.2 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.

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

In addition to the DSMC above, no more than six patients at a time will be permitted to be dosed concurrently. More specifically, we will limit the accrual rate to this such that a maximum of 6 patients at any one time will be in the window between immunotherapy dosing and 10 days post recovery from definitive surgery. All patient safety data for this study will be reviewed by Drs. Divi and/or Colevas, and documented on the AE log. If there are any adverse events (Grade 3 or higher or serious of any grade) attributed to checkpoint inhibitor treatment, further enrollment to the study will be put on hold until the attribution is understood and the protocol has been modified accordingly (with IRB notification and approval) to mitigate the future risks to patients. Our statistical design was powered with the least number of patients necessary to achieve our primary objective. If during the course of the study, the number of patients who fail to complete the neoadjuvant protocol (due to drug related toxicity or tumor progression) is such that the primary objective would be unachievable, the study will be stopped early. Based on our statistical design, if at any point during the study, 4 patients fail to complete the neoadjuvant protocol, the study will be stopped early.

7.2.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

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 cutaneous 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.

7.2.2 Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.2.3 Adverse Events of Special Interest

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor 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 trial Sponsor 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 x ULN in combination with total bilirubin > 2 x ULN
  - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment (STIAMP), 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.

The Atezolizumab Events of Special Interest Are:

- 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)
- Facial Paresis
- Myelitis

7.3 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).

7.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 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.

All adverse events (AEs), regardless of seriousness or relationship to study drug, are to be collected only on designated study dates from signing of informed consent through 30 days after administration of study drug, and recorded in the study-specific worksheets, with the following exceptions:

- AEs that are solely laboratory values; are not related to the study drug; AND are clinically non-significant may not be collected.
- Non serious AEs that are not related to the study drug; are not clinically significant; AND are expected in the post-surgery clinical setting may not be collected.
- SAEs that occur from signing of informed consent to prior to administration of study agent may not be collected unless assessed as possibly, probably or definitely-related to a study procedure.

All patients enrolled in this study receive surgical intervention in the course of their standard of care. As a consequence of this surgery, patients may experience certain

expected and normal adverse events. The following post-operative adverse events will be captured only in the patient's Electronic Health Record (EHR) source documentation and not in the adverse event log. If the adverse event exceeds the grading listed below or occurs outside the post-operative time window, the adverse event will be recorded in the Adverse Event Logs.

- Surgical wound site and associated, expected secondary signs and symptoms, including:
    - CTCAE v5.0 Grade 1 pain associated with surgical wound, including headaches – mild pain, little to no limit on adult daily life.
    - CTCAE v5.0 Grade 1 weight loss, anemia, and electrolyte abnormalities.

7.4 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.

7.5 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.5.1 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?"

7.5.2 Specific instructions for Recording Adverse Events

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

7.5.2.1 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.

7.5.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 7.3.1), 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”.

7.5.2.3 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”).

7.4.2.4 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

7.5.2.5 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age–appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life–threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
[d] Grade 4 and 5 events must be reported as serious adverse events

7.5.2.6 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.

7.5.2.7 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior atezolizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

7.5.2.8 Reconciliation (Case Transmission Verification)

The Investigator agrees to conduct reconciliation for the product. Genentech and the Investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party.

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 Investigator 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 (CTV) report will be sent to Genentech.

7.6 Adverse Event Reporting

The Investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/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 or CIOMS I form, or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, 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
Batch ID/lot ID for biologics associated with AE/SSR/PC/AESI must be included when submitting the case reports to Genentech.
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:

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

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

Other Special Situation Reports
In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to 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

Product Complaints
All Product Complaints (with or without an AE) shall be forwarded to Genentech within thirty (30) 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.

7.6.1 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

7.6.1.1 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

7.6.2 Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech, as the Marketing Authorization Holder, will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

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, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

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.

And to the site IRB:

IRB panel manager
Fax: (650) 725-8013

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

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

7.7 Aggregate Reports

7.7.1 Development Safety Update Report

The Parties agree that aggregate reporting obligations for the Study (including Development

Safety Update Report [DSURs] and/or Investigational New Drug [IND]) Annual Reports) in accordance to the applicable laws and regulations in the concerned countries will reside with the investigator, as the Sponsor of the Study.

Upon request, the investigator agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

Genentech will forward to the investigator an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that the investigator may cross-reference the executive summary of the Genentech DSUR, as applicable.

7.7.2 Other Reports

The Investigator will forward a copy of the Publication to Genentech upon completion of the Study.

7.8 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 Drug Safety CTV oversight mail box at: ctvistsa@gene.com

Queries

Queries related to the Study will be answered by the Investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. The Investigator 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 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.

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 investigator, as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If investigator - 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 investigator - sponsor with signal and risk management activities related to the Product within the Study.

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

Compliance with Pharmacovigilance Agreement / Audit
The Parties 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.

8. CORRELATIVE/SPECIAL STUDIES

Blood collection methods:
Up to 150 ml of blood may be taken for research at baseline, after the first cycle of therapy, and at surgery for a maximum total of 300 ml of blood for research purposes within the period of a month. The blood will be drawn in Vacutainer tubes. These tubes, barcoded labels, and a transport envelope will be provided by the study coordinator(s). The blood will be drawn by a phlebotomist or appropriately qualified person. The tubes will be labeled with the barcode labels placed in an envelope (which will be included with the tubes) and kept at room temperature. A barcode label will also be placed on an intake form that has the patient study ID number. The study coordinator will then be notified of the blood samples and will arrange for transport to the Biobank section of the CTRU.

We will be collecting plasma, serum, and PMBCs from the blood which will be used for the following:

- Plasma samples for exploratory assessment cell-free DNA at baseline, after the first cycle of therapy, and at surgery.

- Serum samples for assessment of cytokine profiles associated with immune system activation.
- Peripheral blood mononuclear cells (PBMC) will be collected and cryopreserved at baseline, after the first cycle of therapy, and at surgery if deemed for possible, for exploratory identification of antigen-specific T cell receptors (TCR).

Tumor sampling methods:
When each patient is enrolled on this study, he or she will be assigned an anonymized bar code for all samples. The study coordinator will link the barcodes to the patient. The key will be kept in REDCap. If archival tissue is unavailable at the time that the patient signs consent, or is deemed unsuitable for exploratory research, a pretreatment biopsy is required. Tumor tissue sample will also be obtained following the first cycle of therapy and at the time of surgical resection, if deemed clinically feasible, for exploratory research on biomarkers. The least invasive technique to obtain the sample will be used. 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) are acceptable. If the tissue collected is fresh, the tissue will be placed in saline on ice, and Dr. Sunwoo's laboratory personnel will be notified.

The 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, peptide-MHC repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, circulating tumor DNA, or RNA, analysis of mutations, genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes, and analysis of proteins. Research will aim to distinguish germline mutations from somatic mutations and understanding mechanisms underlying immune cell recognition of tumor cells that might predict clinical response to therapy. NGS methods may include whole exome sequencing (WES). De-identified biospecimen may be sent to other (external) collaborators.

Please refer to section 4.6 for further information.

9. STUDY CALENDAR

	Screening [a]	Treatment Cycles (21-day cycles)					Surgery	Follow-Up (or Treatment Discontinuation [b])
		Cycle 1		Cycle 2		Cycle 3		
	Within 28 days prior to start of treatment	Day 1 (± 3 days)	Day 14 (± 7 days)	Day 21 (± 3 days)	Day 38 (± 4 days)	Day 42 (± 3 days)	2-4 weeks after Cycle 3	10 days ± 5 days after surgery (or < 30 days after last treatment)
Informed consent	X [c]							
Baseline tumor tissue sample [d]	X							
Second tumor tissue sample, if clinically feasible			X					
Demographic data	X							
Medical history and baseline conditions	X							
Vital signs [e]	X	X		X		X		X
Weight	X	X		X		X		X
Height	X							
Complete physical examination [f]	X							X
Limited physical examination [g]		X		X		X		
Digital Photography	X		X				X	
ECOG Performance Status	X							X
ECG [h]	X							
Hematology [i]	X [j]	X [k]		X		X		X

	Screening [a]	Treatment Cycles (21-day cycles)					Surgery	Follow-Up (or Treatment Discontinuation [b])
		Cycle 1		Cycle 2		Cycle 3		
	Within 28 days prior to start of treatment	Day 1 (± 3 days)	Day 14 (± 7 days)	Day 21 (± 3 days)	Day 38 (± 4 days)	Day 42 (± 3 days)	2-4 weeks after Cycle 3	10 days ± 5 days after surgery (or < 30 days after last treatment)
Chemistry [l]	X [j]	X [k]		X		X		X
Pregnancy test [m]	X [j]							
Coagulation (INR, aPTT)	X [j]							
TSH [n]	X [j]							X
Urinalysis [o]	X [j]							
CT or MRI of primary site (if present) and regional lymphatics	X [p]				X [p] (prior to cycle 3)			
Chest CT with contrast or PET scan	X [p]							
Blood sample for exploratory biomarker research [q]	X		X				X	
Tumor response assessments [s]	X [r]	X [s]		X		X	X	
Concomitant medications [t]	X	X		X		X		X
Adverse events [u]	X [u]	X [u]		X [u]		X [u]		X [u]
Atezolizumab administration [v]		X		X		X		
Surgical resection							SOC	
Adjuvant Therapy [w]								SOC

	Screening [a]	Treatment Cycles (21-day cycles)					Surgery	Follow-Up (or Treatment Discontinuation [b])
		Cycle 1		Cycle 2		Cycle 3		
	Within 28 days prior to start of treatment	Day 1 (± 3 days)	Day 14 (± 7 days)	Day 21 (± 3 days)	Day 38 (± 4 days)	Day 42 (± 3 days)	2-4 weeks after Cycle 3	10 days ± 5 days after surgery (or < 30 days after last treatment)

ADA = anti-drug antibody; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; NA = not applicable; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WES = whole exome sequencing; WGS = whole genome sequencing.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded in the patient's medical records (except in the case of an adverse event).

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to start of treatment may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy will also be performed, when clinically feasible, for biomarker assessment. Refer to Section 4.6 or tissue sample requirements.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline in the patient's medical records. At subsequent visits, record new or worsened clinically significant abnormalities in the patient's medical records. For the first and subsequent infusions, vital signs should be measured prior to the infusion (taken same day during clinic visit or in infusion area) and, if clinically indicated, during or after the infusion.

[f] Record abnormalities observed at baseline in the patient's medical records. At subsequent visits, record new or worsened clinically significant abnormalities in the patient's medical records.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities in the patient's medical records.

[h] ECG recordings will be obtained during screening and as clinically indicated at other timepoints.

[i] Hematology includes WBC count, hemoglobin, hematocrit, platelet count, differential count.

[j] Screening laboratory test results must be obtained within 28 days prior to initiation of study treatment.

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

[m] All women of childbearing potential will have a serum pregnancy test at screening, within 28 days prior to initiation of study treatment.

[n] Past TSH lab value may be used for screening if collected within 6 weeks prior to the first administration of atezolizumab.

[o] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood

[p] Baseline imaging with CT or MRI of primary site (if present) and regional lymphatics; CT Chest or PET scan will be performed only if scans were not previously performed within 28 days of screening assessment. The same radiographic modality used to assess disease sites at screening should be used for subsequent tumor assessment at baseline and after cycle 2. **RECIST measurements are only required at baseline, after cycle 2, and ORR can be assessed after cycle 2/surgery.**

[q] See Section 4.6 for details on exploratory research

[r] 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.

[s] Patients will undergo clinical tumor assessments at baseline and once per cycle. All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. **RECIST measurements are only required at baseline, after cycle 2, and ORR can be assessed after cycle 2/surgery.**

[t] 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 until the treatment discontinuation visit.

[u] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, Genentech, Inc. should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

	Screening [a]	Treatment Cycles (21-day cycles)					Surgery	Follow-Up (or Treatment Discontinuation [b])
		Cycle 1		Cycle 2		Cycle 3		
	Within 28 days prior to start of treatment	Day 1 (± 3 days)	Day 14 (± 7 days)	Day 21 (± 3 days)	Day 38 (± 4 days)	Day 42 (± 3 days)	2-4 weeks after Cycle 3	10 days ± 5 days after surgery (or < 30 days after last treatment)

[v] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[w] Adjuvant therapy will be delivered as per standard of care for head and neck cutaneous squamous cell carcinoma. AJCC Stage 3 and 4 lesions will receive adjuvant radiation therapy beginning 4-8 weeks after the completion of surgery unless the patient is deemed medically unfit, or patient declines further treatment.

10. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

Primary Outcome Measure
Title: Percentage of patients that are able to complete 3 cycles of neoadjuvant therapy and undergo a curative surgical resection.
Time Frame: At time of surgery
Safety Issue: No

10.1 Primary and Secondary Outcome measures

The primary outcome measure for each patient is an indicator for successfully completing 3 cycles of neoadjuvant atezolizumab, followed by surgical resection of remaining disease. The treatment will be evaluated as non-feasible for patients who have disease progression during neoadjuvant treatment, discontinue study medications due to toxicity, or are not able to undergo curative surgical resection after the 3 cycles of treatment. Patients who decline surgical intervention after completing the neoadjuvant treatment will be considered as having successfully received neoadjuvant treatment.

In this study, feasibility was chosen as the primary endpoint to assess whether patients can successfully complete the neoadjuvant treatment without significant disease progression precluding curative surgical resection, and with acceptable toxicity. Since the patient population will include tumors that are resectable at presentation (and patients will be medically fit to undergo surgery), any postponement of definitive surgical resection will need to demonstrate that this does not adversely affect the opportunity for curative therapy. If this postponement of surgery proves to not cause harm and administration of neoadjuvant treatment is feasible, this study may add an additional cohort to evaluate a combination of immune checkpoint inhibitors in this setting. Future studies can be designed that evaluate additional clinical endpoints.

10.1.1 Relevant Subset

All patients that receive at least 1 dose of Atezolizumab will be considered as “evaluable” patients for this feasibility study.

10.2 Secondary Outcome

The overall response rate and pathological response rate (complete and major pathological response) following completion of neoadjuvant therapy will be reported with a 95% exact confidence interval.

Objective response rate will be measured based on RECIST v1.1 criteria (Appendix F). Overall response rate will be determined based on Appendix F, Table 1. Pathological response will be assessed by local pathological review. Patients with no viable tumor seen will be classified as a complete pathological response. Patients with < 10% of viable tumor will be classified as a major pathological response.

The change in surgical margins, vital structures preserved, morbidity, and/or surgical approach will be described qualitatively for each patient in the study and summarized.

10.2.1 Relevant Subset

The objective response rate will be evaluated for all patients that had both sets of imaging (pre-treatment and after cycle 2). All patients that had surgery will be included to assess pathological response rate, change in surgical margins, and vital structures preserved.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

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. The study team will immediately forward to their IRB any written safety report or update provided by Genentech (Investigator's Brochure, safety amendments and updates, etc.).

Atezolizumab is an FDA approved drug for various indications including non-small cell lung cancer, small cell lung cancer, and Alveolar Soft Part Sarcoma (ASPS). etc. Neither the investigator, nor the sponsor, Genentech, Inc. intend to report the study data to the FDA as a well-controlled study in support of a new indication or any other significant change in the labeling for Atezolizumab, nor do we intend, at this time, to utilize the study data to support a significant change in the advertising of atezolizumab. The drug is currently not approved for CSCC; however we believe this study is IND-exempt, for the risks are not expected to be beyond what is seen with the routine SOC use of this agent.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local

standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

This clinical research study will be monitored both internally by the PI and externally by the Stanford University IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the Stanford University 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.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis and safety information including AE's, conmeds collected at the specified timepoints. Case report forms will be developed using the REDCap database system and will be maintained by the clinical trial coordinators. CRFs will be kept in a locked office, only accessible to the research team. The REDCap database for data management will be developed prior to enrollment. The database will be locked 3 months after the last patient visit per study calendar for the primary and secondary analyses.

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 Stanford University IRB.

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.

11.4 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 4.8.

11.5 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.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

The primary objective is to determine the feasibility of three doses of atezolizumab prior to surgery in patients with advanced cutaneous squamous cell carcinoma. Our baseline assumption is that 50% of the population will complete all 3 doses of atezolizumab and then proceed to surgery. We can prove that with 20 patients by showing that 85% of the patients enrolled will complete the 3 neoadjuvant cycles of PD-L1 and then proceed to surgery. We will also be collecting demographic and descriptive data on tumor characteristics, and therapies. Please refer to sections 12.4 to 12.7 for the study's statistical plan.

This approach will be considered feasible if 17 or more patients are able to complete neoadjuvant treatment and proceed with surgical resection of disease. If 4 or more patients are unable to complete neoadjuvant treatment due to toxicity or tumor progression, or have unresectable disease at the time of surgery, this approach will be considered unfeasible. Patients who decline immunotherapy or surgery due to reasons not related to toxicity or tumor progression, will not be considered a treatment failure.

12.2 Randomization

Not applicable.

12.3 Interim analyses

Accrual will be limited to no more than 6 patients at a given window of immunotherapy dosing and 10 days post recovery from surgery. Toxicity and treatment failures will be reviewed prior to each additional patient accrual. If the number of patients who fail neoadjuvant treatment exceeds the maximum number allowable to achieve the primary objective, the study will be stopped early (i.e. treatment failure in 4 patients).

12.4 Descriptive Statistics and Exploratory Data Analysis

Baseline demographic data, tumor characteristics, staging information, and complete treatment data (including surgery and adjuvant therapies), will be recorded and presented at the completion of the trial.

12.5 Primary Analysis

The evaluation of feasibility will be based on percentage of patients completing 3 cycles of neoadjuvant atezolizumab and followed by surgical resection of remaining disease. We expect 85% of patients will fall in feasibility category, leaving only 3 patients unable to complete 3 cycles and undergo surgery. With such a small subsample, instead of using quantitative analysis method, we will develop in-depth, detailed case study aiming to assess the potential differences between these cases and the rest of patients in potential confounders such as patients' demographics, comorbidities, tumor stage, and surgical morbidity.

The change in surgical plan will be recorded by the primary surgeon based on initial assessment of the tumor and the size and location of the tumor at the time of definitive surgical resection.

12.6 Secondary Analysis

Objective response rate will be assessed per investigator assessment and pathological response rate will be assess by local pathology review. The overall response rate and pathological response rate following completion of neoadjuvant therapy will be reported with a 95% exact confidence interval.
The change in surgical margins, vital structures preserved, morbidity, and/or surgical approach will be described qualitatively for each patient in the study and summarized.
For objective response rate, we will look at the response assessment at each cycle for visible lesions and record the greatest dimension. For all lesions, we will also be using RECIST to assess tumor progression and record tumor size from the CT scan which will be done at baseline, and then after cycle 2. For lesions that are not visible, we will only assess response after cycle 2 when an interval set of imaging is performed.
The pathological response rate will be measured by pathologists at the local institution

and be recorded as a percentage of viable tumor remaining. Tumors with 0% viable tumor will be considered a complete pathological response, and tumors with >0% and ≤10% will be classified as a major pathological response. The change in surgical margins will be measured in 3 dimensions by the surgical investigator based on anticipated surgical resection at presentation, and again at the time of surgery. The number of vital structures preserved per patient will be recorded and include >50% of the nose, lip, ear, or eye. These data will be presented in a table format at the conclusion of the study.

12.7 Sample Size

12.7.1 Accrual estimates

Based on the number of patients seen at the Stanford Head & Neck Oncology Clinic there are about 2 patients seen per month who would qualify for this study. We estimate that 8 patients annually will be enrolled in the study, and will require 42 months to complete the study.

12.7.2 Sample size justification

The primary objective is to determine the feasibility of three doses of atezolizumab prior to surgery in patients with advanced cutaneous squamous cell carcinoma. The sample size of evaluable 20 patients allows at least 80% power to reject the null hypothesis of 50% if the true fraction is above 80% (or a difference >30%) using binomial enumeration of all possible outcomes, with a test at the 5% significance level. We expect the true fraction is 85%, which means that we are well powered to detect an effect size that is bigger than 30%.

12.7.3 Effect size justification

The effect size was chosen based on recently published data using immunotherapy for mucosal head and neck cancer demonstrating clinical response in approximately 50% of patients.

12.8 Criteria for future studies

If we meet the endpoint for determining that this approach is feasible, we will move towards designing a larger trial that examines surgical margin reduction, disease recurrence rates, and optimal adjuvant therapy strategies. We may also test the feasibility of this strategy using different combination regimens in the future to further increase response rate and tumor volume reduction.

13. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007;13:1050–9.

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119–35.

Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373;1627–39.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Choueiri TK, Ross RW, Jacobus S, et al. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. J Clin Oncol 2012;30:507–12.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634–46.

DeMets D, Lan KKG. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603. doi: 10.1080/19420862.2015.1136043. Epub: 26 February 2016.

Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277–80.

European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. 2012 Dec. EMA/CHPM/205/95/Rev.4.

[FDA] U.S. Department of Health and Human Services Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007 May.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Fozza C, Corda G, Virdis P, et al. Derangement of the T-cell repertoire in patients with B-cell non–Hodgkin's lymphoma. Eur J Haematol 2014:1–12.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Galand C, Donnou S, Molina TJ, et al. Influence of tumor location on the composition of immune infiltrate and its impact on patient survival. Lessons from DCBCL and animal models. Front Immunol 2012;3(98):1–8.

Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: update and controversies. J Clin Oncol 2006;24:5545–51.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Herbst RS, Baas P, Kim D-W, et al. Pembrollizumab versus docetaxel for previously treated PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387;1540–50.

Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody atezolizumab in cancer patients. Nature 2014; 515: 563–7.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imRECIST): refining guidelines to assess the clinical benefit of cancer immunotherapy. J Clin Oncol 2018. doi: 10.1200/JCO.2017.75.1644 [published online before print 17 January 2018].

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Karia PS, Han J, Schmults CD.Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol. 2013;68(6):957-966.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression-free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. BMJ Open 2013;3:1–6.

Merritt RE, Mahtabifard A, Yamada RE, et al. Cisplatin augments cytotoxic T-lymphocyte-mediated antitumor immunity in poorly immunogenic murine lung cancer. J Thorac Cardiovasc Surg 2003;126:1609–17.

Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;12:528–38.

Postow M, Manuel M, Wong P, et al. T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma. J Immunother Cancer 2014;2(Suppl 3):08.

Powderly JD, Koeppen H, Hodi FS, et al. Biomarkers and associations with the clinical activity of PD-L1 blockade in a atezolizumab study. J Clin Oncol 2013;31:abstract 3001.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rossille D, Gressier M, Damotte D, et al. High level of soluble programmed cell death ligand 1 in blood impacts overall survival in aggressive diffuse large B-cell lymphoma: results from a French multicenter clinical trial. Leukemia 2014;28(12):2367–75.

Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 2006;355:2542–50.

Seymour L, Bogaerts J, Perrone A, et al., on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2107;18:e143–52.

Sonpavde G, Sternberg CN, Rosenberg JE, et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 2010;11:861–70.

Stinchcombe TE, Socinski MA, Lee CB, et al. Considerations for second-line therapy of non-small cell lung cancer. Oncologist 2008;13:128–36.

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. New Engl J Med 2010;363:733–42.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–20.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

References for cutaneous squamous cell carcinoma

Ally, Mina Sarah, et al. "An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma." Journal of the American Academy of Dermatology 71.5 (2014): 904-911.

Ansouri B, Housewright C. The treatment of actinic keratoses—the rule rather than the exception. J Am Acad Dermatol 2017; 153(11):1200.

Blank, Christian U., et al. "Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma." Nature medicine 24.11 (2018): 1655-1661.

Colevas AD, Bahleda R, Braiteh F, Balmanoukian A, Brana I, Chau NG, et al. Safety and clinical activity of atezolizumab in head and neck cancer: results from a phase I trial. Ann Oncol. 2018;29(11):2247–53.

Forde, Patrick M., et al. "Neoadjuvant PD-1 blockade in resectable lung cancer." New England Journal of Medicine 378.21 (2018): 1976-1986.

Gross, N., et al. "Phase II study of neoadjuvant cemiplimab prior to surgery in patients with stage III/IV (M0) cutaneous squamous cell carcinoma of the head and neck (CSCC-HN)." Annals of Oncology 30 (2019): v910.

https://www.cancer.net/cancer-types/skin-cancer-non-melanoma/statistics

Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018; 379:341-351.

Moolenburgh SE, Mureau MA, Versnel SL, Duivenvoorden HJ, Hofer SO. The impact of nasal reconstruction following tumor resection on psychosocial functioning, a clinical-empirical exploration. Psychooncology. 2009 Jul;18(7):747-52. doi: 10.1002/pon.1459.

O'Donnell, Jake S., et al. "The promise of neoadjuvant immunotherapy and surgery for cancer treatment." Clinical Cancer Research 25.19 (2019): 5743-5751.

Radiotis G, Roberts N, Czajkowska Z, Khanna M, Körner A. Nonmelanoma skin cancer: disease-specific quality-of-life concerns and distress. Oncol Nurs Forum. 2014 Jan 1;41(1):57-65. doi: 10.1188/14.ONF.57-65.

Segal NH, Ou S-HI, Balmanoukian A, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: results from a phase I/II expansion cohort. Eur J Cancer. 2019;109:154–61.

Walter A, Barysch MJ, Behnke S, et al. Cancer-testis antigens and immunosurveillance in human cutaneous squamous cell and basal cell carcinomas. Clin Cancer Res. 2010;16:3562-3570.

APPENDICES

APPENDIX A: **Participant Eligibility Checklist**

I. Subject Eligibility Checklist

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	**NEOADJUVANT ATEZOLIZUMAB IN SURGICALLY RESECTABLE ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA**
Protocol Number:	**ENT0082 / IRB-59070**
Principal Investigator:	**Vasu Divi**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion/Exclusion Criteria			
Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Signed Informed Consent Form	☐	☐	
2. Age ≥ 18 years at time of signing Informed Consent Form	☐	☐	
3. Histologically or cytologically confirmed squamous cell carcinoma	☐	☐	
4. Measurable disease per RECIST v1.1 • Note that protocol specified imaging is not necessary to fulfill this criterion. For example, a patient presenting with a visible 4cm primary lesion who has obviously RECIST evaluable disease may be considered eligible prior to baseline imaging stipulated in the protocol.	☐	☐	
5. Availability of a representative tumor specimen that is suitable for determination of PD-L1 immunohistochemical stain evaluation.	☐	☐	
6. ECOG Performance Status of 0 or 1	☐	☐	

Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
7. Adequate hematologic and end-organ function appropriate for surgery as determined by routine preoperative evaluation. If liver function, renal function and hematologic laboratory test results are within limits acceptable for elective surgery. Laboratory results that will need to be obtained within 28 days prior to initiation of study treatment: • AST, ALT, total bilirubin, and alkaline phosphatase (ALP) ≤ 2.5 x upper limit of normal (ULN.). • TSH < 13 o Patients with a history of a high TSH who are receiving levothyroxine replacement at the time of eligibility evaluation and have no clinical evidence of hypothyroidism are eligible.	☐	☐	
8. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen	☐	☐	
9. Negative hepatitis B surface antigen (HBsAg) test at screening	☐	☐	
10. 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 (≥ 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	☐	☐	
11. For men: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below: With a female partner of childbearing potential or pregnant female partner, men must agree to remain abstinent or use a condom during the treatment period and for 5 months after the final dose of atezolizumab to avoid exposing the embryo. Men must agree to refrain from donating sperm during this same period	☐	☐	

Inclusion/Exclusion Criteria

Exclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
1. Patients not eligible for standard of care surgical resection	☐	☐	
2. Distant metastatic disease	☐	☐	
3. 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.	☐	☐	
4. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)	☐	☐	
5. Active or history of autoimmune disease or immune deficiency, 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 (see Appendix G for a more comprehensive list of autoimmune diseases and immune deficiencies), 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: o Rash must cover < 10% of body surface area o Disease is well controlled at baseline and requires only low-potency topical corticosteroids o 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	☐	☐	
6. 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. Active tuberculosis. Patients do NOT have to be screened for tuberculosis for this trial.	☐	☐	
8. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina	☐	☐	

Inclusion/Exclusion Criteria

Exclusion Criteria (From IRB approved protocol)	Yes	No	Supporting Documentation*
9. 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	☐	☐	
10. 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.	☐	☐	
11. Prior allogeneic stem cell or solid organ transplantation	☐	☐	
12. 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	☐	☐	
13. 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 5 months after the final dose of atezolizumab	☐	☐	
14. Current treatment with anti-viral therapy for HBV	☐	☐	
15. Treatment with investigational therapy within 28 days prior to initiation of study treatment	☐	☐	
16. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies	☐	☐	
17. 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	☐	☐	
18. 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 systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study 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.	☐	☐	
19. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins	☐	☐	
20. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation	☐	☐	
21. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of study treatment	☐	☐	

Inclusion/Exclusion Criteria			
Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
• Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.			

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-reporting, and medical record review.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

APPENDIX B: Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Source: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

APPENDIX C: 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 Patient Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX D: FDA MedWatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email.

APPENDIX E: 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

APPENDIX F: Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)

10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

1 For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

Bone Lesions:

Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions:

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

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

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation .

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It

is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

Complete response (CR): Disappearance of all target lesions

Any pathological lymph nodes must have reduction in short axis to <10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

All lymph nodes must be non-pathological in size ($<$10 mm short axis).

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

PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

APPENDIX G: 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-related 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).

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

APPENDIX H: 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:

Stop the study treatment infusion.

Call for additional medical assistance.

Maintain an adequate airway

Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.

Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.

Continue to observe the participant and document observations.

Draw serum/plasma samples for immunogenicity testing.

Ask participant to return for washout immunogenicity sample if appropriate.

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

The 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-related adverse events prior to initiating therapy and throughout treatment and survival 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 for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune- mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate). The decision to rechallenge patients with atezolizumab should be based on the investigator's assessment of the benefits and risks and document by the investigator. The Medical Monitor is available to advise as needed.

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).

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

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

MANAGEMENT GUIDELINES

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. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For 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 and contact the Medical Monitor. [c] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event. •
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial 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 the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and document by the investigator. The Medical Monitor is available to advise as needed.

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

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have 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 2 Management Guidelines for Hepatic Events

Event	Management
In patients without HCC	
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of ≥ 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Consider patient referral to GI 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.

GI=gastrointestinal; HCC = hepatocellular carcinoma; LFT = liver function test; ULN=upper limit of normal.[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 requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased 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 3 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. • 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 Medical Monitor. [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 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 Medical Monitor. [c]

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 determined 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-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by the investigator (or an appropriate delegate).

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor.[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 the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

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 4 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 Medical Monitor 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.
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 and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
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 and contact the Medical Monitor. [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. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
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 Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [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 requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab 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 and contact the Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [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 the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-RELATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table 6.

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. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of 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 6.

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 6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Events	Management
Immune-mediated myocarditis, Grades 2-4 Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or 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 Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretic 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 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

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

Table 7 Management Guidelines for Infusion-Related Reactions and 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 ($\geq$2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, 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, and contact the Medical Monitor. • 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 Medical Monitor.

Event	Management
Grade 3 [a] fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Permanently discontinue atezolizumab the Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • 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 the Medical Monitor. [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. • 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=intraveous; 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 the investigator's benefit-risk assessment and documented by the investigator . For subsequent infusions, administer oral premedication with antihistamines, antipyretic 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

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 8.

Table 8 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 Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 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 Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [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 the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 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 and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [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 the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

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 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related 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, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – 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 Medical Monitor. [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 Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [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 Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

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

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table 1 Management Guidelines for Immune-Mediated Myelitis

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

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Immune-Related Meningoencephalitis

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

RENAL EVENTS

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 12.

Table 13 Management Guidelines for Renal Events

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

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. • 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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

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 possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

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

Table 14 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 Medical Monitor. • 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 Medical Monitor. [c]

Table 14 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • 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 Medical the Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [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 the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[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 rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

- Fever $\geq 38.5°C$
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
    - Hemoglobin $\leq$ 90 g/L (9 g/dL) ($\leq$ 100 g/L [10 g/dL] for infants $\leq$ 4 weeks old)
- Platelet count $\leq 100 \times 10^9$/L (100,000/μL)
- ANC $\leq 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides $\geq$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $\leq$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $\geq$ 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 $\leq 181 \times 10^9$/L (181,000/μL)
    - AST $\geq$ 48 U/L
    - Triglycerides $\geq$ 1.761 mmol/L (156 mg/dL)
    - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; IV=intravenous; MAS = macrophage activation syndrome.

Immune-mediated Facial Paresis

- 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.
- Refer patient to neurologist.
- Initiate treatment as per institutional guidelines.
- Atezolizumab should be withheld for patients with Grade 1 or 2 immune-mediated facial paresis and permanently withdrawn for ≥Grade 3 immune-mediated facial paresis

References

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908-14.