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Phase I/II Study to Evaluate the Safety and Clinical Efficacy of Atezolizumab (aPDL1) in Combination with Temozolomide and Radiation in Patients with Newly Diagnosed Glioblastoma (GBM)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
anti-HBc	antibody to hepatitis B core antigen
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
BSA	body surface area
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CNS	central nervous system
CL	clearance
CR	complete response
CRF	Case Report Form
CRO	contract research organization
CT	computed tomography
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
EC_{50}	50% effective concentrations
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	leucovorin, 5-fluorouracil, oxaliplatin
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
irAE	immune-related adverse event
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction

Abbreviation	Definition
irRC	immune-related response criteria
IV	intravenous
LFT	liver function test
LPLV	last patient, last visit
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PES	polyethersulfone
PET	positron emission tomography
PFS	progression-free survival
PI	Package Insert
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
PUVA	psoralen plus ultraviolet A radiation
PVC	polyvinylchloride
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UBC	urothelial bladder cancer
ULN	upper limit of normal
V_{ss}	volume at steady state

1. INTRODUCTION

1.1 Glioblastoma

Glioblastoma is the most common malignant primary brain tumor in adults and invariably carries a poor prognosis. Despite optimal multimodality treatment that typically includes surgery, radiation, and cytotoxic chemotherapy, recent clinical trials have reported a median overall survival of only 14–16 months with a 26 –33% 2 year survival rate (Stupp et al. 2005, Gilbert et al. 2013)

1.1.1 Current Management

The aggressive nature of glioblastoma (GBM) is based on its infiltrative behavior that makes total resection difficult. Tumor resection of more than 98% does improve the prognosis and is therefore recommended as initial treatment in the management of GBM (Lacroix et al. 2001, Stummer et al. 2008). The next step in management is fractionated external beam RT with a total dose of 60 Gy delivered in 30 fractions (2 Gy/fraction) to the T2/FLAIR hyperintensity area and 2-cm margin with a boost to the contrast-enhancing area, in addition to concurrent chemotherapy over the course of 42 days. Stupp and colleagues introduced the use of temozolomide, an alkylating cytotoxic agent, at a dose of 75 mg/m2 daily during the course of radiotherapy followed by maintenance temozolomide at 150-200 mg/m2 on days 1-5 every 28-day cycle. This regimen prolonged median overall survival (OS) from 12.1 to 14.6 months and increased the 2-year survival rate from 10.4 to 26.5% compared with results for patients who received radiotherapy alone. This regimen demonstrates statistically significant survival benefits and currently remains the standard of care (Stupp et al. 2005).

1.2 Background on Atezolizumab

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

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

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and metastatic non-small cell lung cancer.

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

1.3 Study Rationale

The majority of GBM patients (61%) have tumors with at least 1% or more PD-L1-positive cells, and 38% have at least 5% or greater PD-L1 expression. PD-L1 is commonly expressed on the GBM-infiltrating T cells as well. Expression of both PD-L1 and PD-1 are negative prognosticators for GBM outcome (Nduom et al, 2016). Immunotherapy strategies such as PD-1/PDL-1 inhibition may work synergistically with radiation, which has been shown to increase antigen presentation and promote a pro-inflammatory tumor microenvironment.

In this trial, atezolizumab will be given concurrently with radiation therapy and temozolomide followed by the combination of temozolomide and atezolizumab in the adjuvant stage. During the Phase I component, we will determine the safety of administration of atezolizumab in combination with radiation and temozolomide (concurrent stage) and the safety of atezolizumab in combination with temozolomide (adjuvant stage). If atezolizumab is found to be safe in both the concurrent and adjuvant stages of the Phase I component of this study, we will proceed with Phase II in which a larger number of patients will be treated with atezolizumab in combination with radiation and temozolomide during the concurrent stage and atezolizumab in combination with temozolomide during the adjuvant stage. The Phase II component will obtain preliminary data on efficacy and integrate evaluation of early biomarkers of response to later transition to a pivotal Phase II/III trial.

2. OBJECTIVES

2.1 Primary Objectives

- Phase I: To evaluate the safety of atezolizumab in combination with radiation and temozolomide during the concurrent stage and in combination with temozolomide during the adjuvant stage.
- Phase II: To evaluate the overall survival (OS) of atezolizumab in combination with radiation and temozolomide and in combination with temozolomide at onset of treatment.

2.2 Secondary Objectives

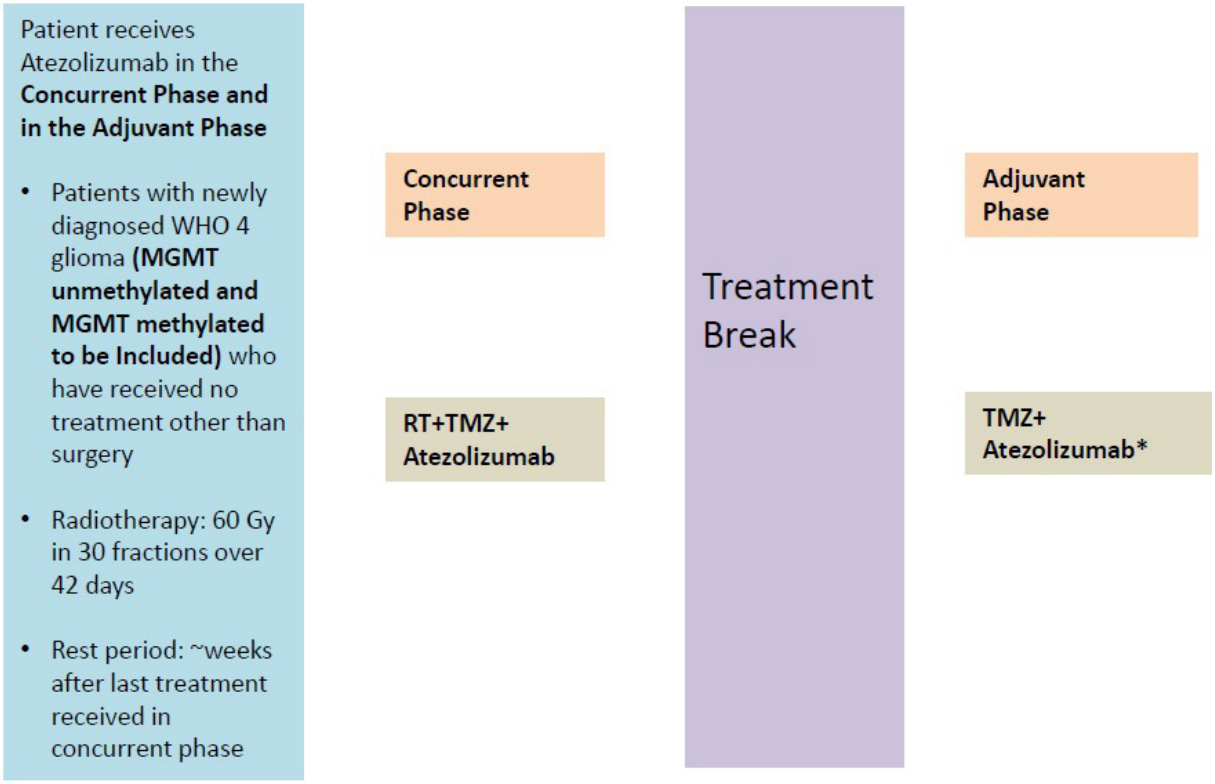
- To evaluate the overall response rate (ORR), duration of response, and progression free survival (PFS) of atezolizumab in combination with radiation and temozolomide during the treatment period.

2.3 Correlative Objectives

- Profiling tumor immune cell populations (example: IHC analyses of CD4, CD8, PD-1, PD-L1, and PD-L2).
- Profiling of tumor; DNA, mRNA, microRNA and epigenetic profiling (DNA methylation) and evaluation of whole exome sequencing, RNA sequencing, microRNA sequencing and cell-free circulating tumor DNA (ctDNA).
- Peripheral blood collection for evaluation of circulating chemokines/cytokines.
- Stool collection for gut microbiome profiling

2.4 Description of the Study

Study schema for both Phase I and Phase II
10 patient safety lead-in during Phase I prior to enrollment for Phase II
50 patients to be enrolled in Phase II for a total of 60 patients



*Up to 12 cycles of adjuvant therapy

This Phase I/II study is expected to accrue 60 patients over 24 months at a rate of 2.5 patients a month.

Assessment of drug safety will be evaluated during Phase I in a total of 10 patients. Once the 10 patients in the safety run-in stage have completed at least one cycle of treatment, the study team will review all clinical data to determine if the expansion stage can be initiated. Following maximal safe surgical resection, patients with newly diagnosed GBM who have received no treatment other than surgery will be eligible for enrollment. Patients will receive radiation consisting of fractionated focal irradiation administered using 1.8-2 Gy/fraction daily x 5 days/week for ~6 weeks for a total dose of up to 60 Gy in combination with low dose daily temozolomide dosed at 75 mg/m^2. During the administration of concurrent chemoradiation, Atezolizumab 840 mg will also be administered every 2 weeks. Following completion of the concurrent stage (radiation + temozolomide + Atezolizumab), the patient will then be placed on a treatment break prior to initiation of the adjuvant stage. The treatment break duration will be 21-28 $\pm$ 2 days at which time a new MRI brain with and without contrast will be obtained. During the adjuvant phase, patients

will then receive temozolomide 150 mg/m^2 days 1-5 every 28 days in combination with Atezolizumab 840 mg every 2 weeks for up to 12 cycles of therapy until there is evidence of disease progression as determined by iRANO criteria. Temozolomide during cycle 2 may be dose escalated to 200 mg/m^2 days 1-5 every 28 days if there is no evidence of toxicity.

If the patient's blood counts are not sufficient enough to begin temozolomide at the start of the adjuvant phase, the patient may proceed with treatment on Atezolizumab 840 mg every 2 weeks alone. When the patient's blood counts are within acceptable parameters, temozolomide can then be added to Atezolizumab in the adjuvant phase. Dosing of temozolomide at a dose no lower than 100 mg/m^2 days 1-5 every 28 days will be permitted for those patients who have evidence of myelotoxicity from treatment.

Radiotherapy Specifications

Radiation target definition for glioblastoma as follows. GTV defined as tumor cavity and any T1 tumor enhancement. CTV will include GTV + 2 cm margin customized to include FLAIR enhancement (if thought by the radiation oncologist to be tumor) and exclude bone, fascia, and other anatomical barriers. PTV-50 will include CTV + 3-5 mm and will be treated to 50 Gy in 30 fractions. PTV-60 boost volume will include GTV + 3-5 mm and will be treated to 60 Gy in 30 fractions.

Treatment will be planned using Pinnacle software system. Planning will be based on non-contrast CT images obtained at time of simulation in addition to MRI scan. Treatment will be delivered using linear accelerator. Fractionated radiation will be delivered daily M-F with weekends off for all patients. IMRT plans use a configuration of five to seven isocentric 6-MV photon beams delivered in a step-and-shoot technique. For inverse planning specified dose constraints are given to organs at risk including the brainstem, spinal cord, optic chiasm, optic nerves, and cochlea (Appendix 6).

Safety Analysis

Toxicity events will be closely monitored during both the Phase 1 (10 patient safety lead-in) and the Phase II (50 patients) portions of the study. NCI CTCAE v4.0 will be used for assessing adverse event severity.

The safety analysis will summarize treatment-event adverse events (TEAEs) for all treated subjects using discrete summaries at the subject- and event-level by system organ class and preferred term. A TEAE will be defined as occurring on or after the day that treatment is initiated. Treatment-related TEAEs, TEAEs leading to death, SAEs, and TEAEs resulting in treatment discontinuation will be summarized similarly. TEAEs will also be summarized by NCI-CTCAE Grade.

All TEAEs occurring during the study will be included in by-subject data listings and tabulated. KPS will be summarized at screening and at study drug discontinuation

Results of laboratory tests, including hematology, chemistry, and urinalysis will be summarized by Cycle (and day) and for change from baseline to the Cycle (and day) using continuous summary

statistics (mean, standard deviation, minimum, median, and maximum). The number of subjects with each NCI-CTCAE grade by Cycle will also be presented. Shift tables will be presented summarizing the shift in NCI-CTCAE grade from baseline to each Cycle. Additionally, summary statistics will be provided for the worst case observation over all Cycles for both continuous and categorical summaries.

Vital signs will be summarized using continuous summary statistics (mean, standard deviation, minimum, median, and maximum) by cycle and day, including change from baseline summaries and worst case summaries.

Study drug exposure will be summarized using continuous summary statistics on the total drug exposure and total days of exposure as well as discrete summary statistics on the number of Cycles of exposure.

Radiographic Analysis: RANO criteria

Traditionally, progression was determined using criteria set forth by Macdonald et al. These criteria relied heavily on changes in contrast enhancement to establish whether a tumor was radiographically stable, improved, or progressed. More recently, given the recognition of the phenomena of pseudoprogression as well as widespread use of anti-angiogenic agents that rapidly affect blood vessel permeability, attempting to establish a diagnosis based on these criteria has led to increasing ambiguity. In recognition of this, the Response Assessment in Neuro-Oncology (RANO) working group has recently put forth updated criteria for establishing treatment response in neuro-oncology patients. These criteria will be used for determining radiographic outcomes for this study. See Appendix 4.

Neurological Exam

Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, (as compared to the baseline assessment), that should coincide with objective measurement of tumor size.

+	Definitely better
+	Possibly better
	Unchanged
-	Possibly worse
-	Definitely worse

Performance Status: Patients will be graded according to KPS (Appendix 5)

Time to Death: From date of registration to date of death due to any cause.

Definition of Overall Response Rate: Number of patients with PR and CR maintained for a minimum of 6 weeks.

Criteria for Removal from Study

Study Treatment Termination

Withdrawal of Subject from Study Treatment
Subjects will be discontinued from further study treatment in the event of any of the following:

- Progression of disease - Patients must be followed by MRI scans, as was used for baseline tumor measurements, and will be removed from study treatment if progression is documented after any cycle of treatment. Patients with stable disease, partial or complete response, or patients experiencing clinical benefit will continue on therapy.
- Unacceptable toxicity includes any life-threatening irAEs atezo-related events or any treatment-related AE that the investigator deems to be detrimental to the patient health.(see Section 4.5)

The patient may withdraw from the study at any time for any reason.

- Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of receiving further therapy.
- Non-compliance by the patient with protocol requirements.
- Patient lost to follow-up. If a patient does not return for a scheduled visit, every effort should be made to re-establish contact. In any circumstances, every effort should be made to document treatment safety, if possible.

All reasons for discontinuation of treatment must be documented in the flow sheets.

2.5 End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 20 months after the last patient is enrolled.

2.6 Rationale for Study Design

The prognosis for GBM is universally poor despite optimized multimodality treatment including surgery, radiation, and chemotherapy. In this trial, atezolizumab is being added to the current standard of care for GBM which has remain unchanged since Stupp et al published their seminal paper in 2005. Therapies that improve survival are desperately needed for GBM. The mechanistic rationale supporting the combination of immunotherapy with chemoradiation is that localized radiation induces cell death and the release of tumor antigens (Tang et al. 2014). A local immune response may have the potential to induce systemic tumor immunity due to an abscopal effect. Localized radiation could stimulate immune-mediated tumor regression even possibly outside the treated radiation field. Immunotherapy strategies such as PD-1/PDL-1 inhibition may work synergistically with radiation, which has been shown to increase antigen presentation and promote a pro-inflammatory tumor microenvironment.

Atezolizumab will be given concurrently with radiation and temozolomide followed by the combination of temozolomide and atezolizumab in the adjuvant stage. During the Phase I component, we will determine the safety of atezolizumab in combination with radiation and temozolomide (concurrent stage) and the safety of atezolizumab in combination with temozolomide (adjuvant stage). The Phase II component will obtain preliminary data on efficacy and integrate evaluation of early biomarkers of response to later transition to a pivotal Phase II/III trial. Although patients regardless of MGMT methylation status will be potentially eligible for enrollment, a separate analysis of methylated versus non-methylated patients will be performed following study completion.

2.7 Outcome Measures

Evaluation of response will be determined according to RANO criteria as described in section 2.4 (Appendix 4: RANO criteria)

3. MATERIALS AND METHODS

3.1 Study Population

3.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability and willingness to comply with the requirements of the study protocol
- Age ≥ 18 years.
- Have histologically confirmed World Health Organization Grade IV glioma (glioblastoma or gliosarcoma). Archival tissue will be required for diagnosis confirmation. Receipt of archival tissue is not required for the start of treatment.
- Patients must have undergone surgery and must not have had any further treatment following surgery.
- Have a performance status of ≥ 60 on the KPS.
- A baseline brain MRI obtained no more than 14 days prior to study enrollment on a stable or tapering dose of steroids no greater than 4 mg a day of dexamethasone for at least 5 days.
- Patients must start treatment within 6 weeks of definitive resection.
- Demonstrate adequate organ function as defined in the following table:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 /mcL

Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN
[a]Creatinine clearance should be calculated per institutional standard.	

- All screening labs should be performed within 14 days (+3 working days) of treatment initiation.
- Female subject of childbearing potential should have a negative serum pregnancy test within 14 days (+ 3 working days) of study enrollment.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the duration of the study. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- Male subjects should agree to use an adequate method of contraception during the course of the study.

3.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.
General Exclusion Criteria:

- Has received prior interstitial brachytherapy, implanted chemotherapy, or therapeutics delivered by local injection or convection enhanced delivery. Prior treatment with Gliadel® wafers will be excluded. Prior treatment with the Optune® device will be excluded.
- Is currently participating or has participated in any other newly diagnosed therapeutic trial before or after chemoradiation.
- Any serious medical condition that interferes with adherence to study procedures.
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0).
- Has known leptomeningeal disease, gliomatosis cerebri, extracranial disease, or multifocal disease. Subject has multifocal GBM, defined as discrete sites of contrast enhancing disease without contiguous T2/FLAIR abnormality that require distinct radiotherapy ports. Satellite lesions that are associated with a contiguous area of T2/FLAIR abnormality as the main lesion(s) and that are encompassed within the same radiotherapy port as the main lesion(s) are permitted.
- Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit.
- Contraindication for undergoing MRIs.
- Inability to comply with study and follow-up procedures.
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
    - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
    - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
    - Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
        - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.
        - Rash must cover less than 10% of body surface area (BSA).

  - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%).
  - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids).
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.
- History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection
  - Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible. Patients will be sampled for HBV DNA and will be referred to a virologist to monitor for HBV re-activation.
  - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Anticipation of need for a major surgical procedure during the course of the study
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study and for 5 months after last dose of atezolizumab.
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score ≤ 6, and prostate-specific antigen [PSA] ≤ 10 mg/mL, etc.)

Patients may not receive concomitant chemotherapy, hormonal therapy, immunotherapy, or radiotherapy while patients are on study.

Medication-Related Exclusion Criteria:

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

- Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN]-α or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1
  - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation

3.2 Study Treatment

3.2.1 Study Drug: Atezolizumab

Atezolizumab will be administered at a flat dose: 840 mg every 2 weeks during the concurrent phase with radiation and temozolomide and during the adjuvant phase in combination with temozolomide at a dose of 840 mg every 2 weeks. This dosage of atezolizumab is equivalent to an average body weight–based dose of 15 mg/kg Q3W. The dosage of 15 mg/kg Q3W was selected as the recommended Phase II dose for atezolizumab on the basis of both nonclinical studies and available clinical data from a Phase I study (PCD4989g), as described below. The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor interstitial concentration–to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging from 0.01 to 20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The MTD of atezolizumab was not reached, and no dose-limiting toxicities were observed at any dose. ATAs to atezolizumab were associated with

changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but patients treated at 10, 15, and 20 mg/kg maintained the expected target trough levels of drug despite the detection of ATAs. To date, no relationship has been observed between the development of measurable ATAs and safety or efficacy. After review of available PK and ATA data for a range of doses, 15 mg/kg Q3W was identified as the lowest atezolizumab dosing regimen that would maintain C_{trough} at ≥ 6 μg/mL while further safeguarding against interpatient variability and the potential for ATAs to lead to subtherapeutic levels of atezolizumab.

The 2 week dosing is being chosen to allow for alignment with 6 week RT/TMZ and 4 week adjuvant TMZ cycles. A 3 week dosing would have placed undue stress on the patient and would have decreased enrollment, increased financial burden on the patient and reduced quality of life due to excessive visits. We believe this dosing schedule will be safe which will be verified through the 10 patient safety lead-in.

3.2.2 Formulation

The atezolizumab 840 mg drug product is provided in a single-use, 15-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 14 mL (840 mg) of ATEZOLIZUMAB solution but may contain more than the stated volume to enable delivery of the entire 14-mL volume. The formulation of atezolizumab 840 mg drug product is identical to that of atezolizumab 1200 mg drug product.

ATEZOLIZUMAB must be refrigerated at 2°C – 8°C (36°F – 46°F) upon receipt until use. ATEZOLIZUMAB vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the ATEZOLIZUMAB drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the ATEZOLIZUMAB Investigator's Brochure.

3.2.3 Dosage, Administration, and Storage

The dose level of ATEZOLIZUMAB to be tested in this study is 840 mg every 2 weeks (equivalent to an average body weight–based dose of 15 mg/kg administered by IV infusion every 3 weeks (21 [± 2] days)). ATEZOLIZUMAB will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between ATEZOLIZUMAB and PVC or polyolefin infusion materials (bags or infusion lines). Administration of ATEZOLIZUMAB will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of ATEZOLIZUMAB will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion, the patient's vital signs (heart rate,

respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of ATEZOLIZUMAB. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.

- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.

- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided in Section 3.5.

3.3 Temozolomide

3.3.1 Temozolomide Formulation

Other Names: - methazolastone; Commercial name is Temodar. Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Dose is rounded to the nearest 5 mg based on surface area. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lauryl sulfate NF.

3.3.2 Mode of Action

Alkylating agent of imidazotetrazinone class.

3.3.3 Storage and Stability

The capsules are packaged in amber glass bottles and should be stored at 25 °C. Temperature excursions between 15 and 30 °C are permissible. Refer to the commercially labeled bottles for expiration dating.

3.3.4 Pharmacokinetics

Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

3.3.5 Metabolism and Elimination

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m2.

3.3.6 Creatinine Clearance

Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide has not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m2).

Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

3.3.7 Hepatically Impaired Patients

In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

3.3.8 Gender

Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

3.3.9 Age

Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of grade 4 neutropenia and grade 4 thrombocytopenia in the first cycle of therapy than patients less than 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

3.3.10 Drug-Drug Interactions

In a multiple dose study, administration of temozolomide with ranitidine did not change the Cmax or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

3.3.11 Adverse Events

Hematologic: Thrombocytopenia, leukopenia, myelodysplastic syndrome
Gastrointestinal: Nausea, vomiting, anorexia
Hepatic: Elevated liver enzymes (reversible)
Skin: Rash
Neurologic: Convulsions, weakness on one side of the body, abnormal coordination, paralysis
Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

Please refer to the temozolomide package insert for a comprehensive list of adverse events.

3.3.12 Special Handling and Precautions

Capsules should not be opened or damaged. Rigorous precautions should be taken to avoid capsule contents having contact with skin or mucous membranes. Capsule contents may be irritating to skin and eyes. Mutagenic and prolonged exposure may cause serious health effects (outside of prescribed dosage in this trial).

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.

3.3.13 Contraindications

Temozolomide is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

3.3.14 Pregnancy Category D

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

3.3.15 Supply

Temozolomide is commercially available and it will be supplied through the patients' insurance provider.

3.4 Concomitant and Excluded Therapies

3.4.1 Concomitant Therapy

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

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

distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with ATEZOLIZUMAB but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered.

Steroid use for IRR prophylaxis should be minimized, however, steroid use for suspected irAEs should be instituted immediately per management guidelines for atezolizumab-specific adverse events outlined in Appendix 11. Systemic corticosteroid use or physiologic replacement doses are permitted even at doses > 20 mg/day prednisone equivalent for treatment related AEs, symptoms related to GBM including management of cerebral edema, or treatment of non-autoimmune conditions (eg, prophylaxis for contrast dye allergy, contact hypersensitivity). Details regarding corticosteroid use prior to and during the study will be collected (name of medication, doses used, start and stop dates, frequency of use, and route of administration).

Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megastrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

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

All concomitant medications will be captured for data and entered into a case report form.

3.4.2 Excluded Therapy

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

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 3.4.1)
  - After Cycle 1, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases); ATEZOLIZUMAB administration may be suspended during radiotherapy.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity

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

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

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

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

Concurrent use of Optune® device during treatment on protocol will be prohibited.

3.5 General Plan to Manage Safety Concerns

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 3.1.1 and Section 3.1.2) and close monitoring (as indicated below). See Section 5 for complete details regarding safety reporting for this study.

Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with ATEZOLIZUMAB, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account (see Section 3.1).

Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Patients will be followed for safety for 30 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 for the list and timing of study assessments). All serious adverse events (SAEs) and protocol-defined events of special interest will be reported to Genentech in an expedited fashion (see Section 5). In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is

lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

3.5.1 Management of Specific Safety Concerns with ATEZOLIZUMAB

Toxicities associated or possibly associated with ATEZOLIZUMAB treatment should be managed according to management guidelines for atezolizumab-specific adverse events (Appendix 11). Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. 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, mycophenolate, or TNFα inhibitors.

Grade 2 irAEs, particularly for pulmonary events will mandate holding treatment with ATEZOLIZUMAB, then restart once irAEs improve to Grade 0 or 1. If irAEs recur, treatment with atezolizumab should permanently discontinue. Refer to Appendix 11 for further details on management considerations for immune-related AEs. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of ATEZOLIZUMAB. ATEZOLIZUMAB should be permanently discontinued in patients with life-threatening irAEs.

3.5.2 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation Please

refer to Appendix 11 for management of atezolizumab-specific immune-related AEs.

ATEZOLIZUMAB treatment will be given as long as the patient continues 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 3.6-3.8.

There will be no dose reduction for ATEZOLIZUMAB in this study. Patients may temporarily suspend study treatment for up to 105 days beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If ATEZOLIZUMAB is held because of AEs for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from ATEZOLIZUMAB and will be followed for safety and efficacy as specified in Section 3.5.1 . Suspension of study treatment will include temozolomide and/or radiation in addition to Atezolizumab.

If a patient must be tapered off steroids used to treat AEs, ATEZOLIZUMAB may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced

to a prednisone dose (or dose equivalent) of ≤ 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of principal investigator.
Any toxicities associated or possibly associated with ATEZOLIZUMAB treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.

Discontinuation of ATEZOLIZUMAB may not have an immediate therapeutic effect, and there is no available antidote for ATEZOLIZUMAB. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or additional immunosuppressants.

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Please refer to the temozolomide package insert for dose reduction guidance during concurrent radiation dosing and adjuvant dosing.

3.6 Patient Discontinuation

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:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator determines may jeopardize the patient’s safety if he or she continues in the study
- Investigator determines it is in the best interest of the patient
- Non-compliance by the patient with protocol requirements.

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 on the appropriate Case Report Form (CRF) of the Prometheus (institutional database). However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

See Section 3.9 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

3.7 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Progression of disease
  In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RANO criteria while receiving atezolizumab will be permitted to continue study treatment if they meet all of the following criteria:
  - Evidence of clinical benefit, as determined by the investigator following a review of all available data
  - Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
  - Absence of decline in ECOG Performance Status that can be attributed to disease progression
  - Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions"
- Unacceptable toxicity includes any life-threatening irAEs atezo-related events or any treatment-related AE that the investigator deems to be detrimental to the patient health.(see Section 4.5)
- Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy
- Patient lost to follow-up. If a patient does not return for a scheduled visit, every effort will be made to re-establish contact.
- All reasons for discontinuation of treatment will be documented in the flow sheets.

The primary reason for study treatment discontinuation should be documented on the appropriate CRF. Patients who discontinue study treatment prematurely will not be replaced.

3.8 Study and Site Discontinuation

Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled

3.9 **Clinical and Laboratory Evaluations**

3.9.1 Study Evaluations

Pretreatment Evaluations

A complete history, physical and neurological examination (to include documentation of the patient's Karnofsky Performance Status (KPS) [Appendix 5]) as well as baseline 1.5 or 3 Tesla MRI shall be performed on all patients. The scan done prior to study entry will be reviewed by the patient's treating physician. The baseline scan should be performed within 14 days (±3 working days) of registration.

Pre-study laboratory tests shall include CBC with differential, sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase and uric acid, TSH, free T3, and free T4, aPTT/INR, T-SPOT.TB test, and serum pregnancy test for women of childbearing potential. A stool sample will also be collected for microbiome profiling. Pre-study laboratory tests must be obtained with 14 days (±3 working days) of registration. Urinalysis will be also done at time of screening. In women of childbearing potential, a serum pregnancy test will be obtained throughout the duration of study treatment.

Evaluation During Study

A brain MRI 21-28 ± 2 days following completion of concurrent stage and then every 8 weeks or after every 2 cycles of adjuvant treatment of Atezolizumab and temozolomide. During the study, a CBC with differential will be checked at time of study enrollment and then weekly during the concurrent phase and on Days 1 and 21 of each cycle during the adjuvant stage. A comprehensive metabolic panel and serum pregnancy test for women of childbearing potential at time of study enrollment and then every 4 weeks prior to each cycle of adjuvant treatment will be checked. Thyroid studies will be checked every 3 cycles. A stool sample will be collected following completion of the concurrent stage of treatment and again 6 months into the adjuvant treatment stage.

A complete history, physical and neurological examination (to include documentation of the patient's Karnofsky Performance Status (KPS) [Appendix 5]) as well as baseline 1.5 or 3 Tesla MRI shall be performed on all patients. The scan done prior to study entry will be reviewed by the patient's treating physician. The baseline scan should be performed within 14 days (± 3 working days) of registration.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, or death, whichever occurs first.

Patients who discontinue study treatment for reasons other than withdrawal of consent will be followed for survival and subsequent ant-cancer therapies approximately every 3 months until

death, loss to follow–up, and withdrawal of consent. During this period, documentation of anti-cancer therapies should include administration start and stop dates.

All patients will be followed for overall survival, when possible.

Patients who discontinue treatment due to progression will be followed for survival at least every 3 months. Patients who come off therapy for reasons other than progression should be followed until progression or institution of new anti-tumor therapy. They should then be followed for survival.

3.9.2 Study Assessments

The flowchart of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

3.9.2.1 Medical History

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), prior cancer therapies and procedures, and all medications used by the patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

3.9.2.2 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

3.9.2.3 Physical Examination

A complete physical examination will be performed at screening and at the treatment discontinuation visit and should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

3.9.2.4 Tumor and Response Evaluation

Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Please see Appendix 1 regarding timing of MRI assessments.

3.9.2.5 Laboratory Assessments

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. Analysis of biomarkers on tumor and blood samples will be performed at a central laboratory or at Genentech.

Local laboratory assessments will include the following (see study flowchart Appendix 1):

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)

- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, CPK, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)

- Coagulation (aPTT and INR) at time of screening

- Pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) at time of screening and prior to each adjuvant cycle

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood) at time of screening

- Thyroid function testing (TSH, free T3, and free T4) every 12 weeks (every 3 cycles)

- Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated
  - HBV DNA test is required for patients who have known positive serology for anti-HBc
  - HCV RNA test is required for patients who have known positive serology for anti-HC

- Microbiome Analysis
  - Stool samples will be collected at 3 timepoints for gut microbiome profiling. These time points will be pre-treatment (prior to the concurrent stage), following completion of the concurrent stage (prior to the start of the adjuvant stage), and 6 months into the adjuvant stage of treatment. Stool samples will be collected using the OMNIgene gut microbiome kit which will be provided to patients with detailed instructions (http://www.dnagenotek.com/US/support/ciOMR200.html).

- Biomarker assays
  - In this study, we plan to analyze tumor and serum samples collected at baseline and during treatment from participants enrolled on the trial to identify potential biomarkers with prognostic and predictive value for outcomes (ORR, OS, PFS and toxicity). We will perform tumor profiling to include tumor DNA, mRNA, microRNA sequencing, epigenetics profiling, and cell-free circulating tumor DNA (ctDNA). Peripheral blood collection for evaluation of circulating chemokines/cytokines will also be assessed pre-treatment (at screening), week 10 (Cycle 1 Day 1, prior to start of adjuvant treatment), week 18 (Cycle 3 Day 1, after 2 cycles of adjuvant treatment) and at disease progression. We will also profile tumor immune cell populations (example: IHC analyses of CD4, CD8, PD-1, PD-L1, and PD-L2). In addition, if a biopsy or surgical resection is performed at the time of potential progression, a tumor sample (block or slides) should also be submitted if sufficient tumor material is available.

- Archival tumor tissue sample
  - Archival tumor tissue samples obtained outside of this study for other purposes will be collected, if available, from all patients (paraffin blocks are preferred, and at least 5 unstained slides + 1 H&E slides are acceptable; in lieu of a paraffin block 15 unstained slides + 1 H&E slide may be submitted; all slides should be at 4μm-thickness and on positively charged slides). The tissue will be used for evaluating PD-L1 status by IHC.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

3.9.3 Treatment Discontinuation Visit

Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit.

3.9.4 Follow-Up Assessments

Physical and neurological examinations (to include documentation of the patient's Karnofsky Performance Status (KPS) [Appendix 5]) as well as follow-up 1.5 or 3 Tesla MRI shall be performed on all patients during follow-up.

Laboratory tests shall include CBC with differential, serum creatinine, bilirubin, SGOT, and serum pregnancy test for women of childbearing potential. Please see Appendix 1 for tests that will be performed during follow-up assessments.

3.9.5 Post-Treatment Evaluations

Physical and neurological examinations (to include documentation of the patient's Karnofsky Performance Status (KPS) [Appendix 5]) as well as follow-up 1.5 or 3 Tesla MRI shall be performed on all patients during follow-up. The determination of follow-up visits will be at the treating clinician's discretion if the patient completes the investigational study treatment.

4. STATISTICAL CONSIDERATIONS

4.1 Statistical Design:

Phase I: 10-patient lead-in
Phase II: 50 patients at 2.5 per month with 9 -month post-accrual follow-up

The primary endpoint is overall survival (OS). We will estimate the OS distribution using the Kaplan-Meier method. The historical median for similar patients is about 15 months. If we successfully extend this by 6 months to 21 months, then we would need at least 9 months of post-accrual follow-up to reliably estimate the median OS. If the median OS is 21 months, with 60 patients accrued at the rate of 2.5 per month and with all patients followed for an additional 9 months after accrual, computer simulations indicate that we would expect to observe about 30 deaths and 95% confidence intervals for the median OS would have a lower half-width of about 6 months. In addition, we can estimate the 1-year OS probability at about 67%with a 95% confidence interval with lower half-width of 11%.

In case the combination turns out to be more toxic than expected we will use Bayesian methods (Thall, 2005) to monitor the toxicity rate continuously (stopping if the probability that the 10-week DLT rate > 30% gets unacceptably high) and in case the combination turns out to be less effective than expected we will use Bayesian methods (Thall, 2005) to monitor OS continuously (stopping if the probability that the median survival is greater than 21 months gets unacceptably low).

References:
Thall PF, Wooten LH, Tannir NM (2005) Monitoring event times in early phase clinical trials: some practical issues. Clinical Trials 2:467-478.

4.2 Statistical Analyses

The objective response rate and the overall toxicity rate will be estimated with exact binomial 95% confidence intervals. Kaplan-Meier curves will be generated for OS, PFS, and DoR and median times and probabilities estimated with 95% confidence intervals. Adverse Events will be tabulated by grade and by their relationship to the treatment. Logistic regression will be used to explore the correlations between response rates and correlative markers. Cox proportional hazard regression

will be explore the correlations between time-to-event outcomes and correlative markers. Changes in correlative markers over time will be analyzed by Wilcoxon signed rank tests for pairs of times and linear mixed effects models more generally. Data graphs will be generated to visualize data distributions as well as relationships between variables.

4.3 Toxicity Monitoring Plan

We will monitor time to DLT continuously using a Bayesian method (Thall et al, 2005, Clinical Trials, 2:467-478) that assumes the median time to DLT follows an Inverse Gamma distribution and that the individual times to DLT follow an exponential distribution. Let mE represent the median in the newly accrued (experimental) patients and let mS represent the median to be used for comparison. For the comparison median we specify an Inverse Gamma prior with mean = 19.43 weeks and SD = 0.10 weeks – essentially a constant 30% 10-week toxicity rate. For the experimental median we specify an Inverse Gamma prior with mean of 19.43 weeks and SD = 10.0 weeks. The maximum sample size is 60 and the expected accrual rate is 2.5 per month. Monitoring will be continuous with the rule to stop if Pr(mE > mS | data) < 0.05 . The operating characteristics were computed using One-Arm Time-to-Event Simulator version 3.0.2. The rule will be implemented using the Department of Biostatistics Clinical Trial Conduct website.

Operating Characteristics

10w DLT Rate	Median (w)	PET (%)	Ave # Pts
20%	31.06	0	60
30%	19.43	17	54.79
35%	16.09	54	44.47
40%	13.57	88	31.05
45%	11.59	99	22.43
50%	10.00	100	17.59

Where PET = probability of early termination

4.4 Futility Monitoring Plan

We will monitor time to death continuously starting with the 10th patient using a Bayesian method (Thall et al, 2005, Clinical Trials, 2:467-478) that assumes the median time to death follows an Inverse Gamma distribution and that the individual death times follow an exponential distribution. Let mE represent the median in the newly accrued (experimental) patients and let mS represent the historical median to be used for comparison. Based on historical data the median death time is about 15 months. For the historical median we specify an Inverse Gamma prior with alpha = 58.25 and beta = 858.75 (which has mean = 15.0 and SD = 2.0). For the experimental median we specify an Inverse Gamma prior with alpha = 4.25 and beta = 48.75 (which has a mean of 15.0 and SD = 10.0). The maximum sample size is 60 and the expected accrual rate is 2.5 per month. Monitoring will be continuous with the rule to stop if Pr(mE > mS + 6 | data) < 0.05. The operating

characteristics were computed using One-Arm Time-to-Event Simulator version 3.0.2. The rule will be implemented using the Department of Biostatistics Clinical Trial Conduct website.

Operating Characteristics

Median (m)	PET (%)	Ave # Pts
12	95	25.72
15	73	35.57
18	47	44.32
21	28	50.23
24	16	54.12
27	10	55.86

Where PET = probability of early termination

4.5 Definition of Dose-Limiting Toxicity (DLT)

A DLT is defined as a clinically significant adverse event considered at least possibly related to study drug and meets any of the criteria below during the first 10 weeks of study treatment. If a participant comes off for reasons other than a dose-limiting toxicity during the DLT period, he/she will be replaced. Toxicity monitoring will be continuous during treatment.

Dose limiting toxicities are defined below. A DLT must have an attribution of possible, probable, or definite to experimental study drug and meets the below criteria. For patients experiencing a DLT during the safety lead-in portion of the study, study drug must be discontinued.

- Hematological toxicities will be considered dose limiting if any of the following occur (grade 3 or 4 lymphopenia will not be considered a DLT):
  - ANC of < 500/mm3 for > 7 days
  - Platelets < 25,000/mm^3 for > 48 hours or platelets < 50,000/mm^3 with clinically significant bleeding
  - ≥ Grade 3 febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.3°C)
  - Any hematologic toxicity that prevents administration of atezolizumab for > 28 days

- Non-hematological toxicities will be considered dose limiting if any of the following occur:
  - Inability to complete ≥ 75% of RT due to toxicity related to or exacerbated by Atezo added to Radiation Therapy.
  - Grades 3-4 severity, with the following exceptions:
    - Nausea, vomiting, and diarrhea without sufficient prophylaxis
    - Grade 3 hyperglycemia lasting ≤ 4 days (with optimal medical management) and grade 4 hyperglycemia lasting < 12 hours (with optimal medical management)
    - ≥ grade 3 rash of the acneiform or maculopapular type for no more than a 4 day duration (with optimal medical management)

    - Grade 3 electrolyte disturbances that are asymptomatic and that respond to replacement or intervention (e.g. IV fluids) within 48 hours
    - Grade 3 neurologic toxicity responding within two weeks to steroids, anticonvulsants, or electrolyte correction
    - A subject's first episode of deep venous thrombosis (DVT) or pulmonary embolism will not require dose modification or be considered a DLT since this is very common in glioblastoma patients
- Grade 4 or higher skin rash and oral lesions
- Grade 3 or higher liver Function (AST/ALT/total bilirubin)
- Grade 4 or higher renal function (serum creatinine)
- Grade 3 or higher diarrhea/colitis; Grade 2 diarrhea/colitis with symptoms persistent > 14 days and requiring steroids
- Grade 4 or higher pancreatitis (amylase/lipase); Grade 3 with development of symptomatic pancreatitis or DM;
- Grade 4 pneumonitis; Grade 2 if lymphocytic pneumonitis and symptoms not improving or worsening after 2 weeks of steroids and dose delay; Grade 3 if lymphocytic pneumonitis;
- Grade 4 or higher other GI N-V; Grade 3 and symptoms not resolving within 7 days with symptomatic treatment
- Neurologic events: Grade 2 with steroids required; Grade 3 or higher; any CNS events including aseptic meningitis, encephalitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis
- Grade 3 or higher endocrine hypophysitis and adrenal insufficiency
- Grade 4 or higher fever
- Grade 2 uveitis/ocular lesion
- Grade 3 or higher infusion reaction
- Grade 4 all other immune-mediated events

5. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to ATEZOLIZUMAB, all events of death, and any study-specific issue of concern.

Adverse events of special interest in this study include seizures, cerebral edema, and worsening of focal neurologic deficits following initiation of study treatment.

5.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related AEs, specifically the induction or enhancement of autoimmune

conditions. Refer to the Atezolizumab Investigator's Brochure Section 6 for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.2 Safety Parameters and Definitions

5.2.1 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 patient that emerge during the protocol-specified AE reporting period, including signs or symptoms 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
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

The PI or designee will be responsible for assigning attribution of adverse events to the study agent.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

5.2.2 Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

SAEs will be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

5.3 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 the study drug (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 patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab; 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., pre-existing 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 study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

5.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

5.4.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

5.4.2 Specific Instructions for Recording Adverse Events

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

5.4.2.1 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.

5.4.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.2.2), 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." Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.2.2) that are attributed by the investigator solely to progression of disease should be recorded only in the study CRF.

5.4.2.3 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.4.2.4 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 patient 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 patient 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 pre-existing 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.

5.4.2.5 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or 5 months after the last dose of study drug. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF.

5.4.2.6 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of temozolomide. Temozolomide is genotoxic, and men should not father children for at least 6 months after the last dose of temozolomide. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the pregnancy report via eSAE application with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.2.7 Abortions

Any spontaneous abortion should be classified as an SAE, recorded on the Adverse Event CRF.

5.4.2.8 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF.

5.4.2.9 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient 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 patient who participated in the study, this should be reported as an SAE.

5.4.2.10 Safety Reconciliation

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 monthly 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.

5.4.2.11 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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

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

- Suspected transmission of an infectious agent by the study treatment, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
-

5.4.2.12 Investigator Communications with Genentech

Investigators must report all SAEs to Genentech within the timelines described below. The completed MD Anderson Cancer Center internal electronic serious adverse event (eSAE) reporting form should be sent immediately upon completion to Genentech Drug Safety at:

E-mail: usds_aereporting-d@gene.com
OR
Fax: (650) 238-6067

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

SAE and AESI reports, whether related or unrelated to ATEZOLIZUMAB, will be transmitted to Genentech within 24 hours of the Awareness Date.

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the ATEZOLIZUMAB and within the follow-up period (for female patients within one year after the last dose of ATEZOLIZUMAB or the partner of a male patient within three months of completing therapy), abortions and congenital anomalies/birth defects will be transmitted to Genentech within 24 hours of the Awareness Date.
- All non-serious ATEZOLIZUMAB AEs originating from the study will be forwarded Genentech quarterly.

Note: Investigators should also report events to their IRB as required.

Follow-Up Information

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

- Adding to the original MD Anderson Cancer Center internal eSAE reporting form and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MD Anderson Cancer Center internal eSAE reporting form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE 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.)
- Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

6. STUDY MEDICAL MONITORING REQUIREMENTS

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

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,

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

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

6.1 Study Medication Accountability

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

6.2 Compliance with Law, Audit and Debarment

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

6.3 Quality Management System

Quality assurance measures are provided by three mechanisms: ongoing in-house monitoring of protocol compliance, on-site audits, and response reviews. Data monitoring will begin at the time of patient registration and will continue during protocol performance and completion. The Protocol Manager will perform the ongoing in-house protocol compliance monitoring with the support of the study investigators.

6.4 Data Management

All subjects will be registered in CORe and data will be entered in Prometheus/CORe, the institutional electronic case report form (CRF). Designated research staff will enter the data. All investigators will record information regarding on study, course (flowsheet), off-study, survival, and toxicity data.

All data will be monitored on an ongoing basis by the PI(s), the research study nurses, and data managers. Institutional Review Board (IRB) will be notified of any adverse events and provided data to permit a safety review of the study treatment. The IRB may request additional meetings or safety reports as deemed necessary. The IRB may also stop the trial following a review of results from such analysis.

Data Sharing:

Study data will be shared with Kristin R Swanson, Ph.D at Mayo Clinic (5777 East Mayo Boulevard, Phoenix, AZ 85054) for data analysis. A Material Transfer Agreement will be initiated with Mayo Clinic to transfer data between sites.

Study data will not be shared with any individuals or entities without an IRB approval. Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. All data will be de-identified with access to the linking table available only to the MD Anderson PI and his/her designees. Data submitted to external sites will only be shared in a de-identified fashion. This data will be used only for research purposes.

7. REFERENCES

1. Bellmunt J, Petrylak DP, Powles T, et al. Inhibition of PD-L1 by ATEZOLIZUMAB leads to clinical activity in pts with metastatic urothelial bladder cancer (UBC). Ann Oncol 2014;25 (Suppl 4):iv280–iv304.
2. Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti–CTLA-4 antibodies across clinical indications. Semin Oncol 2010; 37:499–507.

Appendix 1 Study Flowchart

	Screening		**Chemoradiation/Concurrent Phase** (+/-2 days)							**Adjuvant C1-12** (+/-2 days)				Treatment discontinuation visit *	Follow-Up **
Day	<30	<14	1	8	15	22	29	35	42	1	21				
Informed consent	x														
Demographic data		x													
General med history & baseline conditions		x								x				x	
Vital signs [a]		x	x	x	x	x	x	x	x	x				x	
Weight & height (height BL only)		x								x				x	
Physical examination Including KPS		x	x	x	x	x	x	x	x	x				x	
Laboratory tests [list each lab category separately, as shown below]															
Hematology [b]		x	x[b]	x	x	x	x	x	x	x	x			x	
Chemistry [c]		x	x	x	x	x	x	x	x	x				x	
Coagulation (aPTT and INR)		x													
Thyroid function (TSH, free T3, free T4 (*q 3 cycles)		x								x				x	
Urinalysis		x													
Serum pregnancy test (WOCBP)[g]		x	x[g]							x				x	
T-SPOT.TB test		x													
Hepatitis [e]															
Drug administration (Temozolomide) daily during radiation, then days 1-5 of each adjuvant 28 day cycle. Atezolizumab q2 weeks (+/-2 days) during concurrent and adjuvant phase			x	x	x	x	x	x	x	x					

	Screening		**Chemoradiation/Concurrent Phase** (+/-2 days)							**Adjuvant C1-12** (+/-2 days)				Treatment discontinuation visit *	Follow -Up **
Day	<30	<14	1	8	15	22	29	35	42	1	21				
Brain MRI [d]		x								x				x	
Biomarker assays [f]		x								x[f]				x	
Stool collection [h]		x [h]							x [h]				x [h]		
Concomitant medications		x	x	x	x	x	x	x	x	x				x	
Adverse events			x	x	x	x	x	x	x	x				x	

[a] Heart rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Vital signs will be performed within 60 minutes before, during (every 15 [+/- 5] minutes), and 30 (+/- 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion.
[b] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells). Hematology will not be repeated on Day 1 of concurrent phase if done within 14 day at screening.
[c] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.
[d] Response assessment by MRI. Imaging may occur up to 72 hours prior to scheduled day. Baseline assessment must occur within 14 days prior to day 1 of chemoradiation. MRI will be performed 3-4 weeks after completion of concurrent phase (prior to adjuvant phase) and then every 8 weeks or after every 2 cycles during adjuvant phase.
[e] Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) will be performed as clinically indicated
[f] (See Section 3.9.2.5 and Appendix 10) Submission of archival tumor material will be required. Peripheral blood collection for evaluation of circulating chemokines/cytokines will also be assessed pre-treatment (at screening), week 10 (Cycle 1 Day 1, prior to start of adjuvant treatment), week 18 (Cycle 3 Day 1, after 2 cycles of adjuvant treatment) and at disease progression.
[g] Pregnancy test will not be repeated on Day 1 of concurrent phase if done within 72 hours at screening.
[h] Stool will be collected at three time points using the OMNIgene gut microbiome kit prior to the start of the concurrent phase of treatment, at the end of the concurrent phase (prior to the start of the adjuvant phase), and 6 months into the adjuvant phase.

*Treatment discontinuation visit within 30 days (+/-2 weeks) after the last treatment – may be the same as the visit progressive disease was determined
**Follow up visits for patients other than disease progression (e.g., toxicity) will be at the discretion of the treating clinician, including Physical/neurological exam, MRI scan, CBC with differential, serum creatinine, bilirubin, SGOT, and serum pregnancy test for women of childbearing potential. All patients will be followed for survival every 3 months (+/-2 weeks).

Appendix 2 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

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

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

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

Appendix 3 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 4: RANO criteria

Traditionally, progression was determined using criteria set forth by Macdonald et al. These criteria relied heavily on changes in contrast enhancement to establish whether a tumor was radiographically stable, improved, or progressed. More recently, given the recognition of the phenomena of pseudoprogression as well as widespread use of anti-angiogenic agents that rapidly affect blood vessel permeability, attempting to establish a diagnosis based on these criteria has led to increasing ambiguity. In recognition of this, the Response Assessment in Neuro-Oncology (RANO) working group has recently put forth updated criteria for establishing treatment response in neuro-oncology patients. These criteria will be used for determining radiographic outcomes for this study and are outlined below.

Note: As the therapeutic basis of immunotherapy involves the induction of an inflammatory response in the tumor microenvironment, it is often challenging to properly evaluate radiological responses. The appearance of measurable clinical activity at the tumor site may take longer for immunotherapies than for cytotoxic therapies; responses to immunotherapies may occur after conventional progressive disease (tumor burden increase in MRI scans), and immune based therapies may be associated with increased edema and associated T2/FLAIR changes which may inaccurately be interpreted to represent tumor progression

1. PD will require confirmation by resection or a second scan at least 4 weeks apart, provided that the patient remains clinically stable or improves rapidly with a dose of steroids below 2 mg of dexamethasone. This category will be classified as “Unconfirmed PD”. If tumor resection or a subsequent scan confirms the presence of recurrent tumor, the date of PD will be the date of the first scan that showed “Unconfirmed PD”.

2. For those patients who are not candidates for surgical resection and confirmation of PD, these guidelines will be followed:

2.1 Imaging assessment should be repeated 4 weeks later in order to confirm PD with the option of continuing treatment as described below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued / resumed. If repeat imaging confirms PD, defined as a 25% increase from baseline or best response, then the date of PD will be the first date the subject met criteria for progression and subjects will be discontinued from study therapy. Subjects who have confirmed PD will discontinue study medication and enter the follow up/survival phase of the study. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

2.2 In subjects who have initial evidence of radiographic PD (“Unconfirmed PD”), it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the subject’s overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- The subject is believed to demonstrate clinical benefit from the study regimen as determined by the treating physician;
- The subject is adequately tolerating study therapy.
- The subject remains clinically stable or improves rapidly with a dose of steroids below 2 mg of dexamethasone.

When feasible, subjects should not be discontinued until radiographic PD is confirmed. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after receiving RT, but with subsequent disease response. Subjects that are exhibiting significant neurologic decline are not required to have repeat imaging for confirmation of PD.

1. Baseline definitions

a) Measurable Lesions: Enhancing lesions that can be measured bi-dimensionally.

b) Multicentric Lesions: For multicentric lesions that are *discrete foci of enhancement*, the approach is to measure each separately enhancing lesion that meets the inclusion criteria and then calculate the sum of the products.

Lesions that are considered multicentric (as opposed to continuous) are lesions where there is normal intervening brain tissue between the two (or more) lesions. If there is no normal brain tissue between these two (or more) lesions, they will be considered the same lesion.

c) Non-Measurable Lesions: All other lesions that do not meet the criteria for measurable disease as defined, as well as all non-enhancing and other truly non-measurable lesions, are considered non-measurable.

A non-measurable lesion will include foci of enhancement that are less than the specified smallest diameter, non-enhancing lesions seen on T2-weighted or FLAIR images, hemorrhagic or predominantly cystic or necrotic lesions, and leptomeningeal tumor. Hemorrhagic lesions often have intrinsic T1-weighted hyperintensity that could be misinterpreted as enhancing tumor, and for this reason, the pre-contrast T1-weighted image must be examined to exclude baseline or interval sub-acute hemorrhage.

2. Response Definitions

a) Complete response (CR). Requires *all* of the following

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
- No new lesions
- Stable or improved non-enhancing (T2/FLAIR) lesions
- Patients must be off corticosteroids (or on physiologic replacement doses only)
- Stable or improved clinically

Note: Patients with non-measurable disease only cannot have a complete response; the best response possible is stable disease.

b) Partial response (PR). Requires *all* of the following:

- >50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks
- No progression of non-measurable disease
- No new lesions
- Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan
- The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at the time of baseline scan
- Improved or stable clinically

Note: Patients with non-measurable disease only cannot have a partial response; the best response possible is stable disease.

c) Stable disease (SD). Requires all of the following:

- Does not qualify for complete response, partial response, or progression
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

d) Progression. Defined by any of the following:

- >25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*.
- Any new lesion
    - Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose
    - Failure to return for evaluation as a result of death or deteriorating condition
    - Clear progression of non-measurable disease

Note: All measurable and non-measurable lesions must be assessed using the same techniques as at baseline (only MRI allowed in this trial).

*Stable doses of corticosteroids include patients not on corticosteroids.

e) Best Response: This will be calculated from the sequence of objective statuses. For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status. If the response does not persist at the next regular scheduled MRI, the

response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained (i.e. still present on the subsequent MRI) it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

Appendix 5: Karnofsky Peformance Status (KPS)

KPS Score	Criteria
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death no imminent
20	Very sick; hospitalization necessary; active support treatment is necessary

Appendix 6: Dose limitations to critical structures

Below is a list of dose constraints to critical structures. Every effort should be made to achieve these normal tissue constraints.

Structures	Radiation therapy dose
Brainstem	V60Gy < 0.01cc and V55Gy < 0.5cc and V30 < 33%
Brain	V30Gy < 50%
Chiasm	Max dose < 54Gy
Cochlea (Left)	Max dose < 45Gy and mean < 30Gy
Cochlea (Right)	Max dose < 45Gy and mean < 30Gy
Eye (Left)	Max dose < 40Gy and mean < 30Gy
Eye (Right)	Max dose < 40Gy and mean < 30Gy
Len (Left)	Max dose < 5Gy
Len (Right)	Max dose < 5Gy
Optic Nerve (Left)	Max dose < 54Gy
Optic Nerve (Right)	Max dose < 54Gy

In addition, bilateral hippocampal contours will be manually generated on the fused planning MRI CT image set by the treating physician. These contours should be generated as performed in RTOG 0933.

Appendix 7: Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.

Appendix 8 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

GENENTECH SUPPORTED RESEARCH
AE/SAE FAX No: (650) 238-6067
E-mail: usds_aereporting-d@gene.com

Page 1 of

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/_____/_____ dd / mmm / yyyy
Follow-up Report Date	_____/_____/_____ dd / mmm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	- -

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555
PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

Appendix 9 MD Anderson SAE Form

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center	**Internal SAE Report Form for Prompt Reporting** **Institutional Review Board** Submit to: Office of Protocol Research, Unit 1437

Internal Adverse Events that are Serious, Unexpected and Related will require prompt reporting. MDACC IRB requires SAEs that meet the prompt reporting requirement to be submitted to OPR within 5 working days except Death. Deaths that are unexpected and definitely, probably or possibly related to study intervention that occur during and within 30 days after the last day of active study intervention will need to be reported within 24 hours.

Is adverse event serious ☐ Yes ☐ No Is adverse event unexpected ☐ Yes ☐ No Is adverse event related ☐ Yes ☐ No	Name of PI: _____ Department: _____ Unit #_____ PI's Phone: _____
Did the subject die? No ☐ Yes ☐ If Yes, provide date _____ & attribution/relation: _____	PI Signature: _____ Signature Date: _____
Medical Record # _____ Accession # _____ Subject Initials _____ Gender _____	Protocol # _____ Protocol Title: _____
Name of person completing this form_____ Phones # _____	**Status:** Active ☐ Pending Activation ☐ Terminated ☐ CNPE (Pts on tx) ☐ CNPE (Pts off tx) ☐
Initial Report ☐ Follow-up Report ☐ Event/Reaction Onset Date _____ Follow up Date (if applicable) _____	Date Research Team became aware of SAE _____ Date IRB notified _____

SAE/Reaction (Use terms from NCI CTC Terminology)	Grade	Attribution:
_____	_____	Definite ☐ Probable ☐ Possible ☐
_____	_____	Definite ☐ Probable ☐ Possible ☐
_____	_____	Definite ☐ Probable ☐ Possible ☐
_____	_____	Definite ☐ Probable ☐ Possible ☐
Provide brief summary:		

Are these events in the risk section of the ICD? No ☐ Yes ☐ Does the ICD need revision? No ☐ Yes ☐ Should current/previously enrolled subjects be notified of these SAEs? No ☐ Yes ☐		
Is current condition being treated with Investigational agent? No ☐ Yes ☐		
Other Relevant Medical History _____		
List/Attach Relevant Tests, Notes and Lab Data _____		
List/Attach all Concomitant Meds Subject is taking _____		
Name of Agent or Device (list manufacturer and lot)	_____	Did reaction abate after stopping the drug? No ☐ Yes ☐ N/A☐ Date (if yes)_____

		Did reaction reappear after reintroduction? No ☐ Yes ☐ N/A☐ Date (if yes) _____	
Dose (list frequency or schedule)	_____	route of administration	_____
		date(s) of administration	_____
Have you also reported this reaction to the manufacturer? No ☐ Yes ☐			
OPR STAFF: _____ Date returned to PI _____ for: ☐ Incomplete form ☐ Signature missing ☐ Incorrect information ☐ Other ☐ Report during Continuing Review			

Note: With this new form no need to attach the risk section of the ICD

Appendix 10 Laboratory Manual

1. Samples Collection and Processing:

1.1. Archival Tissue

A minimum of 6 slides (5 unstained + 1 H&E) should be submitted, but preference would be 15 unstained slides + 1 H&E. All slides should be at 4μm-thick, and on positively charged slides.

1.2 Biopsy of Surgical Resection Tissue Sample at time of Progression

Paraffin block is preferred; 15 unstained slides + 1 H&E are acceptable. In addition, 2 cryovials of snap frozen tumor (~200mg each; totaling 400mg).
These samples will be processed as follows:
FFPE: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hours post fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples). The FFPE sample is important as it also provides a histological confirmation for the presence and cellularity of tumor cells.
Snap Frozen: Tissue samples measuring ~200mg each should be enclosed in a sterile cryovial and then immediately submerged in liquid nitrogen, and stored in liquid nitrogen tank until time of shipping.

1.3. Blood Specimens:

60 ml of blood (2 streck tubes + 4 EDTA tubes) will be collected at the following time points:

- Pre-treatment
- Week 10 +/- 1 week (this would coincide with the patient's first visit with imaging following completion of RT + TMZ + Atezo)
- Week 18 +/-1 week (this would coincide with a patient visit again with imaging following 2 cycles of adjuvant TMZ + Atezo)
- Disease progression

For: a) isolation of germ-line DNA from peripheral mononuclear blood cells (PMBCs) and TCR-T-cell receptor repertoire; b) isolation of plasma for cell free DNA analysis of genomic abnormalities using gene panels or analysis of cytokines associated with T-cell activation; and, c) potential flow cytometry analyses for phenotypic and functional studies.

2. Biomarker Analysis:

2.1. Histology evaluation of tumor tissue:

H&E-stained sections will be used to confirm the presence of tumor cells, as well as their abundance (tumor cellularity), stromal components and lymphocytic infiltrates. Hematoxylin and

eosin (H&E)-stained sections will be scanned in Aperio™ digital pathology scanner analysis for pathological evaluation and selection for biomarker analysis.

From the tumor tissue specimens, the following pathological analysis will be performed: 1) tumor diagnosis using the World Health Organization (WHO) classification; 2) lowest degree of tumor differentiation; 3) percentage of areas of necrosis; 4) percentage of areas of fibrosis; 5) percentage of viable tumor tissue; and, 6) percentage of viable malignant cells.
Central Review: The scanned H&E-stained slides will be available for pathology analysis at the Translational Molecular Pathology and Biomarker Lab chaired by Dr. Ignacio I. Wistuba, MD Anderson Cancer Center.

2.2. Quality Control (QC) of tumor tissue:

All tissue specimens collected will be reviewed by reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells; b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned and digital images will be available for review.

2.3. Immunohistochemistry (IHC) and Immunofluorescence (IF) analyses:

Fresh frozen and FFPE tissues will be used for analysis of immune markers. For immunohistochemistry (IHC) and multiplex immunofluorescence (IF) analyses, histology sections obtained from FFPE samples will be utilized (Figure 1). IHC and IF will be performed using autostainers. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software; IHC analysis will be performed using the Aperio Image Toolbox™ (Leica Biosystems) and IF analysis using, among pthers, the Vectra Inform™ (Perkin-Elmer) software. The following markers will be performed using optimized and validated protocols, as follows:

IHC assays: Staining of tumor tissue for PD-L1 will be conducted before and after treatment and be performed using the proper IHC assay. Briefly, 4μm-thick histology sections will be used for IHC will be performed on autostainers (Leica Bond Max, Leica Biosystems, Vista, CA). All antibodies have been optimized for IHC by examination of positive and negative controls and testing of the antibodies by Western blotting. To perform quantitative image analysis if the expression of each marker, all IHC slides will be scanned into a digital image scanner (Aperio™ AT Turbo, Leica Biosystems, Buffalo Grove, IL), and analyzed using the Aperio Image Genie Toolbox™ software (Leica Biosystems, Buffalo Grove, IL). Five random 1-mm square areas within the tumor region will be selected for analysis. The expression of IHC marker(s) in malignant cells will be evaluated using the Aperio™ digital H-score system which includes the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300. The expression of markers in inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area.

Multiplex IF Analysis: Up to 20 immune markers distributed in 3-4 panels will be utilized. For multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. The expression of protein markers and inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. The data and digital images will be deposited in a central database for review by pathologists. Among other markers, we will study the expression of the following CD3, CD4, CD8, PD-L1, PD-1, FOXP3, CD45RO, CD57, CD68, and Granzyme B; additional markers will be selected according the results of the gene expression analysis and may include other immunotherapy targets (e.g., OX-40, Vista, GITR, TIM-3, LAG-3, NKp46/CD16, etc.) and proliferation markers (e.g., Ki67).

2.4. Nucleic acids and protein extraction:

Blood (plasma and PMBCs), tumor (CNB and surgical excision specimens) samples will be subjected to DNA, RNA and protein extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses. Also, protein lysate will be extracted using standard methods.

2.5. Molecular analysis of tumor tissues:

Using FFPE and/or fresh frozen for surgical excisions (Figure 1), the following analysis will be performed:

Immuno-oncology (IO) gene expression signatures: Using FFPE tumor tissues, IO panels of genes will be examined using the Nanostring technology (nCounter). This assay will be used to measure expression levels of drug targets, tumor infiltrate composition, and total immune cell composition using a single section of FFPE tumor tissue. The Nanostring methodology offers a cost-effective way to analyze the expression levels of up to 800 genes simultaneously, with precision superior to qPCR. The current Nanostring PanCancer Immune Profiling Panel includes 770 genes and combines markers for 24 different immune cell types and populations, 30 common cancer antigens and genes that represent all categories of immune responses including key checkpoint blockade genes. Alternatively, we will apply the HTG Edge Seq technology, also known as quantitative nuclease protection assay or HTG Edge Chemistry that enables extraction and amplification-free quantitation of mRNA from FFPE tissues without RNA extraction. Their Immuno-Oncology Assay examines the expression of 549 genes implicated in the host immune response to tumors.

Next Generation Sequencing (NGS) analysis: To study tumor molecular abnormalities, fresh, and alternatively, FFPE tumor tissues before and after treatment will be examined for targeted gene panel NGS (analysis of mutations, copy number, indels, translocations), whole exome sequencing (WES) and RNA sequencing. Targeted NGS: Different sequencing platforms can be used to sequence DNA extracted from clinical samples. These platforms have a minimum input of 10ng of sample which make it amenable to sequencing with minimal DNA. The panels available are, among others, CMS50, CMS400, Oncomine and Foundation Medicine. They range from 50 to 409 oncogenes and tumor suppressor genes, with coverage of hotspots and whole exomes. All these

platforms are available at facilities at MD Anderson Cancer Center. WES and RNA-seq: Illumina Hi-seq platform is available at the Sequencing Facilities at MD Anderson Cancer Center

2.6. Flow cytometry Analysis:

This type of analysis may be applied to two types of specimens.

Cryopreserved PBMCs**:** High order flow cytometry panels are available for analysis of tumor tissue and blood specimens. The panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFNγ, TNFα, GB) and 3) defining the expression level of costimulatory and co-inhibitory molecules on T cells. The proposed studies may be conducted retrospectively on cryopreserved PBMCs.

Briefly, 40 cc of peripheral blood from patients:
- Pre-treatment
- Week 10 +/- 1 week (this would coincide with the patient's first visit with imaging following completion of RT + TMZ + Atezo)
- Week 18 +/-1 week (this would coincide with a patient visit again with imaging following 2 cycles of adjuvant TMZ + Atezo)
- Disease progression

And will be processed fresh (within 24h of being drawn) for PBMC isolation. PBMCs will be cryopreserved and stored in liquid nitrogen until use.

Flow cytometry of freshly disaggregated tumor tissue. In selected cases, fresh tissue will be available for flow cytometry analysis. Tumor tissue will be stored in HBSS for up to 24h before processing for flow cytometry. Fresh tissue will be mechanically disaggregated or digested according to needs and panel design. The cells will be processed as a single cell suspension and stained according to each customized panel.

2.7. Liquid biopsy analysis:

Liquid biopsies are non-invasive blood tests that detect tumor cell free DNA (cfDNA) that are shed into the blood from the primary tumor and from metastatic sites. cfDNA testing offers the opportunity to take serial samples in order to monitor tumor genomic changes in real time. There are several platforms available at MD Anderson Cancer Center, including the application of droplet digital PCR (ddPCR) platform in a small panel of hot spots/genes or a larger panel of genes using NGS platform.
Briefly, 20 cc of peripheral blood from patients drawn into 2 x 10mL K2-EDTA tubes:
- Pre-treatment
- Week 10 +/- 1 week (this would coincide with the patient's first visit with imaging following completion of RT + TMZ + Atezo)
- Week 18 +/-1 week (this would coincide with a patient visit again with imaging following 2 cycles of adjuvant TMZ + Atezo)
- Disease progression

And will be processed the same day they are drawn for plasma isolation. Processing details can

be found in the lab manual.

2.8. TCR receptor repertoire:

TCR sequencing analysis may be performed using DNA from tumor tissues as well as PBMC. Briefly, 500 ng tumor DNA or 3-6 ug PBMC DNA will be subjected to high throughput TCR Vβ CDR3 sequencing on an Illumina HiSeq sequencer with at least 5-fold coverage by ImmunoSEQ™ sequencing (Adaptive Biotechnologies, Seattle, WA). TCR profile generated from treatment-refractory tumors at the time of disease progression will be compared to data from pre-treatment tumor samples to explore the TCR repertoire evolution of these tumors under therapeutic pressure. The dynamic changes of TCR from PMBC, when longitudinal blood samples are available, will be correlated to response to immune checkpoint blockade or chemotherapy and survival.

2.9. Cytokines analysis:

For the detection of soluble factors in plasma we may use the SQ120 instrument from Meso Scale Discovery (MSD). This and other technologies allow for the detection of up to 40 analytes per well and uses a very low sample volume, with a sensitivity up to 1000 fold higher than traditional ELISA assays with a large linear range of 3-4 logs. These technologies can be utilized for either single agent detection or in multiplex format.

Appendix 11
Management of Atezolizumab-Specific Adverse Events

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate)

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

1.1.1.1 Event	1.1.1.2 Management
1.1.1.3 Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
1.1.1.4 Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • 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. • For recurrent events, treat as a Grade 3 or 4 event.
1.1.1.5 Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

1.1.1.6 BAL

6. [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 ≤ 10 mg/day oral prednisone or equivalent.
7. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
8. [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.

HEPATIC EVENTS

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

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

1.1.1.7	Event	1.1.1.8 Management
1.1.1.9	Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
1.1.1.10	Hepatic event, Grade 2	**1.1.1.11 All events:** • Monitor LFTs more frequently until return to baseline values. **1.1.1.12 Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]

– LFT

9. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.
10. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
11. [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 by the investigator (or an appropriate delegate).

Table 2 Management Guidelines for Hepatic Events (cont.)

1.1.1.13	Event	1.1.1.14 Management
1.1.1.15	Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

– LFT

12. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.
13. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
14. [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).

GASTROINTESTINAL EVENTS

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

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

1.1.1.16	Event	1.1.1.17 Management
1.1.1.18	Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
1.1.1.19	Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist –2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
1.1.1.20	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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]

– GI = gastrointestinal.

15. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.
16. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
17. [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.)

1.1.1.21	Event	1.1.1.22 Management
1.1.1.23	Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event 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.

18. GI = gastrointestinal.
19. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.
20. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
21. [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.

ENDOCRINE EVENTS

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

1.1.1.24 Event		1.1.1.25 Management
1.1.1.26	Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
1.1.1.27	Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
1.1.1.28	Asymptomatic hyperthyroidism	**1.1.1.29 TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **1.1.1.30 TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
1.1.1.31	Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab. c

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

22. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.

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

24. [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 4 Management Guidelines for Endocrine Events (cont.)

1.1.1.32 Event		1.1.1.33 Management
1.1.1.34	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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
1.1.1.35	Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4		• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

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

25. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.

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

27. [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 both the investigator (or an appropriate delegate).

Table 4 Management Guidelines for Endocrine Events (cont.)

1.1.1.36 Event		1.1.1.37 Management
1.1.1.38	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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
1.1.1.39	Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

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

28. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.

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

30. [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).

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

1.1.1.40	Event	1.1.1.41 Management
1.1.1.42	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.
1.1.1.43	Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab [c]
1.1.1.44	Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

31. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.
32. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
33. [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).

IMMUNE-RELATED MYOCARDITIS

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. 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 GI 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.

Table 6 Management Guidelines for Immune-Related Myocarditis

1.1.1.45	Event	1.1.1.46 Management
1.1.1.47	Immune-related myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
1.1.1.48	Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. c
1.1.1.49	Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] • 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.

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

35. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator .

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

37. [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).

INFUSION-RELATED REACTIONS

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

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions

1.1.1.50	Event	1.1.1.51 Management
1.1.1.52	IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
1.1.1.53	IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
1.1.1.54	IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab. [a]

– IRR

38. [a] 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).

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

1.1.1.55	Event	1.1.1.56 Management
1.1.1.57	Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
1.1.1.58	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 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]

39. GI = gastrointestinal.
40. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.
41. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
42. [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 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

1.1.1.59	Event	1.1.1.60 Management
1.1.1.61	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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
1.1.1.62	Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event 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.

43. GI = gastrointestinal.
44. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.
45. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
46. [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).

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

1.1.1.63 Event		1.1.1.64 Management
1.1.1.65	Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
1.1.1.66	Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
1.1.1.67	Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
1.1.1.68	Dermatologic event, Grade 4	• Permanently discontinue atezolizumab. [c]

47. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time will be determined by the investigator.
48. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
49. [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).

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

1.1.1.69	Event	1.1.1.70 Management
1.1.1.71	Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
1.1.1.72	Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
1.1.1.73	Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Initiate treatment as per institutional guidelines.
1.1.1.74	Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

50. [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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be determined by the investigator.
51. [b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
52. [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).

IMMUNE-RELATED MENINGOENCEPHALITIS

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

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

1.1.1.75 Event		1.1.1.76 Management
1.1.1.77	Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event 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.

53. [a] 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 b the investigator (or an appropriate delegate).