TWO-ARM PARALLEL PHASE 2 CLINICAL TRIAL OF ATEZOLIZUMAB WITH/WITHOUT LOW DOSE, LOCAL RADIOTHERAPY (2 X 2GY) IN PATIENTS WITH RELAPSED/REFRACTORY ADVANCED STAGE FOLLICULAR LYMPHOMA

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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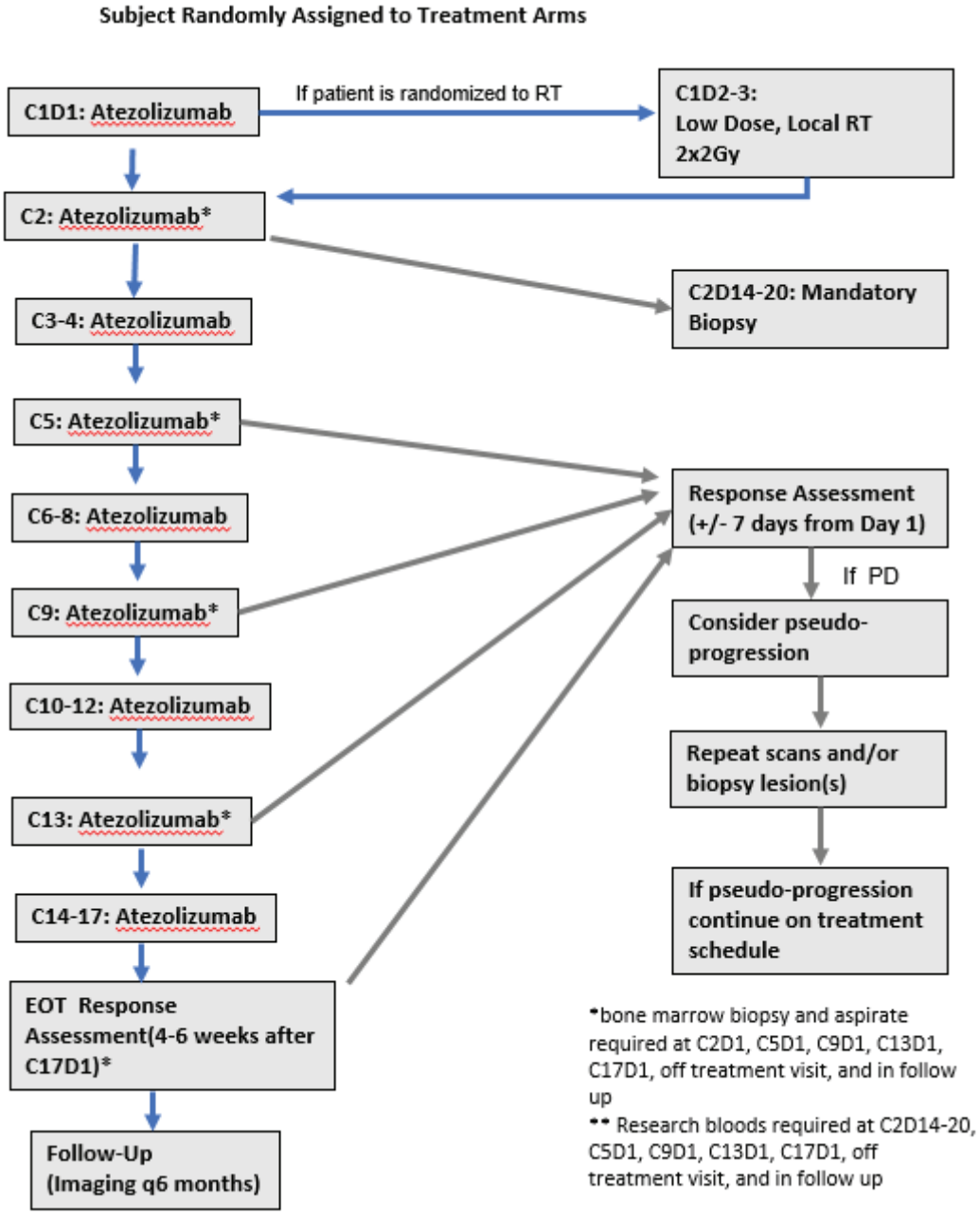
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a two-arm, parallel, open-label, phase II clinical trial designed to assess the efficacy and safety of atezolizumab alone and of atezolizumab in combination with low-dose local radiotherapy in patients with relapsed or refractory follicular lymphoma.

Fifty patients will be enrolled at an estimated accrual rate of 3 patients per month, and will be randomly assigned to receive atezolizumab alone or atezolizumab and local, low-dose radiotherapy.

See Figure 1 for Study Schema.

Figure 1: Study Schema



2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

To determine the objective response rate of either atezolizumab alone or atezolizumab with low-dose, localized radiotherapy (2 x 2 Gy, on Day 2 & 3) to single site of disease in patients with relapsed/refractory advanced stage follicular lymphoma requiring therapy (as measured in the non-irradiated sites of disease).

2.2 Secondary Objectives

To determine the progression-free survival and overall survival of atezolizumab alone and of atezolizumab with low-dose, localradiotherapy (2 x 2 Gy, on day 2 & 3) in patients with relapsed/refractory advanced stage follicular lymphoma requiring therapy

To assess the safety of atezolizumab alone or atezolizumab with low-dose, localized radiotherapy in patients with relapsed/refractory advanced stage FL grade I-IIIA.

2.3 Exploratory Objectives

To determine if clinical responses to atezolizumab are associated with preexisting tumor antigen restricted effector T cells or the development of a more clonal T-cell receptor (TCR) repertoire, and we will determine what impact the addition of concurrent local, low-dose radiotherapy has on TCR diversity and clinical responses.

Using immunohistochemistry, multiplex immunofluorescence, and fresh tissue immunophenotyping with pre-treatment and on-treatment tissue samples and peripheral blood, aim to assess biomarkers related to PD-L1 and/or immune cell biology and tumor biology that might contribute to our understanding of the mechanism of response to PD-L1 therapy and of the abscopal effect of radiation therapy in follicular lymphoma.

Perform a preliminary assessment of the prognostic value of minimal residual disease (MRD).

To determine what impact treatment with atezolizumab and the addition of concurrent local, low-dose radiotherapy has on peripheral blood cytokine/chemokine levels.

3.0 BACKGROUND AND RATIONALE

3.1 Natural History and Current Management of Follicular Lymphoma

Follicular lymphoma is the most common subtype of indolent non-Hodgkin lymphoma in the Western hemisphere and is associated with follicle center B cells that typically contain the translocation t(14:18), which leads to overexpression of the intracellular anti-apoptotic protein Bcl-2.

The clinical course of follicular lymphoma is characterized by remission and relapse (Gallagher et al. 1986). Early-stage indolent follicular lymphoma may be effectively treated with radiation therapy, but patients with advanced disease are not usually cured with conventional treatment.

The disease initially responds to radiation, single-agent rituximab, and/or combination immunochemotherapy, but patients eventually suffer multiple relapses distinguished by increasing refractoriness and decreasing duration of objective response in subsequent lines of therapy. Patients ultimately die from recurrent disease, infection, or treatment-related toxicity. A previous phase II trial evaluated the combination of an anti-programmed death-1 receptor (PD-1) antibody, pidilizumab, in combination with rituximab in patients with relapsed follicular lymphoma (Westin et al. 2013). Patients received intravenous (IV) pidilizumab 3 mg/kg every 4 weeks for 4 infusions and rituximab 375 mg/m^2 IV weekly for 4 weeks starting 17 days after the first infusion of pidilizumab.

Patients with stable disease or better after 4 infusions of pidilizumab received up to 8 additional infusions every 4 weeks for a total of 12 doses. The combination of pidilizumab and rituximab was well tolerated, with no autoimmune or treatment-related adverse events (AEs) of Grade 3 or 4. The most common Grade 1 AEs were anemia (14 patients) and fatigue (13 patients), and the most common Grade 2 AE was respiratory infection (5 patients). Of the 29 patients evaluable for activity, 19 (66%) achieved an objective response: CRs were noted in 15 (52%) patients and partial responses (PRs) in 4 (14%).

In a multicenter phase I study of PD-1 blockade with nivolumab in relapsed/refractory hematologic malignancies, an ORR of 40% was observed (including 1/10 CR and 3/10 PR) among patients with follicular lymphoma (Lesokhin et al. 2015).

In a multicenter phase 1b study of atezolizumab combined with obinutuzumab in patients with DLBCL or FL, there was preliminary evidence that the combination was well tolerated, and an ORR of 21.4% (3/14) and CRR of 14.2% (2/14) was observed at the first response assessment (after cycle 4) among patients with relapsed/refractory FL, with 6 additional patients with FL had stable disease (Palomba et al. 2016).

These data demonstrate that PD-L1 blockade with ATEZOLIZUMAB might safely and effectively induce clinical responses in patients with follicular lymphoma.

3.2 Radiotherapy Background

Radiotherapy is an established treatment modality in the management of patients with non-Hodgkin lymphoma. Indolent non-Hodgkin lymphoma (e.g. FL, MZL, CLL/SLL) and mantle cell lymphoma (MCL) are exquisitely radiosensitive. Nonetheless, radiation doses ranging from 36 to 45 Gy were historically used for the treatment of these histologies based on outdated dose-response studies with questionable methodologies.

A randomized study from the United Kingdom [Lowry et al, 2011] compared the historical standard radiation dose of 40-45 Gy to 24 Gy in 361 subjects with indolent non-Hodgkin lymphoma, mostly comprised of early stage FL and MZL. At a median follow-up of 5.6 years, there was no demonstrated loss of efficacy associated with reduced radiotherapy doses of 24 Gy. No differences were observed in the rates of objective response or within radiation field progression, and there was no difference in progression-free survival and overall survival. 24 Gy is therefore the recommended dose for most patients with early stage follicular lymphoma.

In follicular lymphoma, responses have been described using doses at low as 0.75 Gy. Based on case reports of patients achieving durable local disease control following 4 Gy in 2 fractions, as well as a number of small case series confirming that 4 Gy in 2 fractions is an effective dose in follicular lymphoma, a phase III randomized non-inferiority trial from the UK [Hoskin et al, 2014] compared low-dose radiotherapy (4 Gy in 2 fractions) and conventional dose radiotherapy (24 Gy in 12 fractions) in patients with follicular lymphoma or marginal zone lymphoma having local radiotherapy for definitive or palliative local control. The primary endpoint was time to local disease progression. A total of 614 sites in 548 patients with FL (and some with MZL) were prospectively randomized to receive either low-dose radiotherapy (4 Gy in 2 fractions) or conventional dose radiotherapy (24 Gy in 12 fractions).

The intent of radiotherapy was palliative and definitive in 60% and 40% of subjects, respectively. Conventional dose radiotherapy with 24 Gy was superior. However, low-dose radiotherapy (4Gy in 2 fractions) was associated with minimal toxicity and achieved high rates of local tumor control (44.3% CR, 29.8% PR). Therefore low-dose radiotherapy (4 Gy in 2 fractions) is considered an appropriate approach when the goal of radiotherapy is palliative.

In patients treated with an intratumoral TLR9 agonist, induction of circulating tumor reactive cytotoxic T lymphocytes (CTLs) and responses at distant sites was only observed with concurrent low-dose, local radiotherapy with 4Gy in 2 fractions [Brody et al, 2010]. This dose and fractionation is therefore sufficient to induce both local disease control and a systemic immune response in patients with follicular lymphoma.

Follicular lymphoma (FL) is an indolent but incurable disease with a variable course, and most patients with relapsed/refractory FL ultimately die of their disease. There is a significant need for alternative therapeutic strategies in FL, and one therapeutic target is the inhibitory receptor PD-1. PD-1-triggered T-cell suppression is critical to modulate T-cell response to antigens, but results in pathologic immune tolerance in the tumor microenvironment (TME). A recent phase I study of nivolumab in relapsed/refractory lymphoid malignancies demonstrated that PD-1/PD-L1 blockade is active in FL, with a 40% overall response rate [Lesokhin et al, 2014]. The experience with atezolizumab in FL is encouraging, although with short follow up (See Section 1.2.2.3).

T-cell infiltrates and their spatial distribution within the TME are important predictors of outcomes in FL [Dave et al, 2004; Ame-Thomas et al, 2012; Ame-Thomas et al, 2014; Ansell et al, 2013; De Jong et al, 2011]. Gene expression profiling of FL has shown that immune response signatures of non-malignant cells in the TME are the strongest predictor of outcomes [Dave et al, 2004]. Tumor-infiltrating lymphocytes (TILs) in the FL microenvironment upregulate PD-1 and show diminished responses to antigens and cytokines in a manner that can be reversed by treatment with a PD-1 blocking antibody [Myklebust et al, 2013]. While FL cells do not generally express PD-L1 and PD-L2, PD-L1 is expressed on infiltrating macrophages, which co-localize with PD-1+ tumor-infiltrating T cells.

PD-L1/PD-1 blockade therapy interrupts adaptive immune tolerance of cancer tissues through activation of tumor reactive CTLs, and it has recently been shown that clinical response to PD-1 blockade therapy in melanoma is associated with the presence of clonal expansion of preexisting tumor antigen-restricted CTLs within the TME [Tumeh et al, 2014]. The mechanisms of clinical response to PD-1/PD-L1 blockade in FL are not fully understood.

There is a need for novel combination strategies to augment the activity of PD-1/PD-L1 blockade in FL. In addition to its direct cytotoxic effects, radiotherapy (RT) initiates immunogenic cell death of tumor cells via multiple mechanisms. RT leads to the release of tumor antigen into the TME, translocation of calreticulin to the tumor cell membrane, and release of endogenous adjuvants (e.g. HMGB1, uric acid, heat shock proteins), which in turn lead to the recruitment of dendritic cells, cross presentation of tumor antigens by dendritic cells, and cross priming of tumor CTLs [Vatner et al, 2014].

The combination of RT and either PD-1 or PD-L1 blockade is synergistic in mouse models of colorectal cancer, melanoma, and breast cancer, with improved tumor control and survival, and induction of a durable tumor-specific response and resistance against tumor re-challenge [Dovedi et al, 2014]. Because concurrent RT and PD-1/PD-L1 blockade resulted in synergistic effect on survival whereas sequential therapy did not (RT administered 5 or 7 days prior to PD-1/PD-L1 blockade) [Dovedi et al, 2014], investigators testing the combination of RT and immune checkpoint blockade should limit the time interval between RT and the initiation of immune checkpoint blockade. The addition of local RT to CTLA4 blockade increased the density and diversity of tumor antigen restricted CTLs in a breast cancer mouse model [Pilones et al, 2015].

Low-dose local radiotherapy (RT) with 4Gy in 2 fractions induces durable local disease control without significant toxicity [Hoskin et al, 2014], and has been shown to induce an abscopal effect in patients with FL, with patients treated with the intratumoral TLR9 agonist CpG inducing circulating tumor reactive CTLs and achieving responses at distant sites only with concomitant low-dose irradiation [Brody et al, 2010]. This dose and fractionation of RT is therefore safe and sufficient to induce a systemic immune response in patients with relapsed/refractory, advanced stage FL.

We therefore hypothesize that a radiotherapy-induced systemic immune response can augment atezolizumab activity in patients with advanced stage FL.

3.3 Background of Atezolizumab

Atezolizumab (ATEZOLIZUMAB) is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. ATEZOLIZUMAB was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. ATEZOLIZUMAB targets human PD-L1 and inhibits its interaction with its receptor, PD-1. ATEZOLIZUMAB also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

ATEZOLIZUMAB is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

3.3.1 Summary of Nonclinical Experience

The nonclinical strategy of the ATEZOLIZUMAB program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with ATEZOLIZUMAB.

The safety, pharmacokinetics, and toxicokinetics of ATEZOLIZUMAB were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of ATEZOLIZUMAB for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant

nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of ATEZOLIZUMAB.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for ATEZOLIZUMAB supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

Refer to the ATEZOLIZUMAB Investigator's Brochure for details on the nonclinical studies.

3.3.2 Clinical Experience with Atezolizumab

3.3.2.1 Ongoing Clinical Studies

Current studies of ATEZOLIZUMAB include one ongoing Phase Ia monotherapy study, three ongoing combination studies, five Phase II studies, and one Phase III study. Details of all ongoing studies can be found in the ATEZOLIZUMAB Investigator's Brochure.

Phase Ib Study BO29563

A phase 1b study of PD-L1 blockade with atezolizumab in combination with the anti-CD20 monoclonal antibody obinutuzumab in patients with relapsed/refractory follicular lymphoma and diffuse large B-cell lymphoma is ongoing. This combination appears well-tolerated, and significant clinical activity has been observed among patients with relapsed/refractory follicular lymphoma, with an ORR of 21.4% (3/14) and CRR of 14.2% (2/14) and 6 additional patients with stable disease at the first response assessment after cycle 4 (Palomba et al. 2016).

3.3.2.2 Clinical Safety

Study PCD4989g, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, provides the majority of data (with 558 safety-evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications. The most common cancer types for these patients include NSCLC, urothelial bladder cancer, melanoma, and renal cell carcinoma. Safety data for NSCLC are also derived from Studies GO28625 (FIR) and GO28753 (POPLAR).

Adverse Events

Of the 558 patients with available safety data, 520 (93.2%) experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly

reported events (reported in ≥ 10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough (see Table 1).

Table 1 Study PCD4989g: Adverse Events with Frequency ≥ 10% of Patients for All Grades

Preferred Term	All Grades n (%)	All Grades Related n (%)	Grade 3 4 n (%)	Grade 3 4 Related n (%)
Any adverse event	520 (93.2)	376 (67.4)	239 (42.8)	66 (11.8)
Fatigue	192 (34.4)	115 (20.6)	13 (2.3)	6 (1.1)
Decreased Appetite	142 (25.4)	62 (11.1)	4 (0.7)	0 (0.0)
Nausea	136 (24.4)	65 (11.6)	5 (0.9)	2 (0.4)
Pyrexia	117 (21.0)	63 (11.3)	2 (0.4)	0 (0.0)
Constipation	116 (20.8)	8 (1.4)	2 (0.4)	0 (0.0)
Cough	113 (20.3)	11 (2.0)	1 (0.2)	1 (0.2)
Dyspnea	112 (20.1)	18 (3.2)	18 (3.2)	4 (0.7)
Diarrhea	110 (19.7)	53 (9.5)	2 (0.4)	1 (0.2)
Anemia	104 (18.6)	26 (4.7)	23 (4.1)	5 (0.9)
Vomiting	96 (17.2)	28 (5.0)	3 (0.5)	2 (0.4)
Asthenia	88 (15.8)	53 (9.5)	8 (1.4)	4 (0.7)
Back Pain	85 (15.2)	9 (1.6)	8 (1.4)	1 (0.2)
Headache	83 (14.9)	32 (5.7)	2 (0.4)	1 (0.2)
Arthralgia	79 (14.2)	35 (6.3)	2 (0.4)	0 (0.0)
Pruritus	75 (13.4)	55 (9.9)	0 (0.0)	0 (0.0)
Rash	73 (13.1)	53 (9.5)	0 (0.0)	0 (0.0)
Abdominal Pain	63 (11.3)	12 (2.2)	8 (1.4)	0 (0.0)
Insomnia	62 (11.1)	7 (1.3)	1 (0.2)	0 (0.0)
Peripheral edema	59 (10.6)	7 (1.3)	↓	↓
Chills	57 (10.2)	31 (5.6)	0 (0.0)	0 (0.0)

Note: '↓' refers to missing Common Terminology Criteria grade.

Grade 3 4 adverse events (on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 (NCI CTCAE v4) were reported in 239 patients (42.8%), of which 66 (11.8%) were considered related. Grade 3 and Grade 4 adverse events considered treatment related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

Refer to the Atezolizumab Investigator's Brochure for details on adverse events observed in patients treated with atezolizumab monotherapy or in combination with other agents.

Immune-Mediated Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, gastrointestinal, and respiratory events.

Refer to the Atezolizumab Investigator's Brochure for details on immune-mediated adverse events that were observed in patients treated with atezolizumab. Guidelines for the management of immune-mediated adverse events are described in the Atezolizumab Investigator's Brochure.

For additional information, refer to the Atezolizumab Investigator's Brochure.

3.3.2.3 Atezolizumab Clinical Activity

As of the data cutoff of 1 January 2014, efficacy analyses were performed on 386 efficacy evaluable patients who were defined as those patients, with measurable disease at baseline, treated by 1 July 2013 in Study PCD4989g (to ensure that each patient had a minimum of 6 months follow-up). Patients with multiple tumor types were included in the study, with the largest cohorts consisting of patients with NSCLC, RCC, and bladder cancer. Objective responses with ATEZOLIZUMAB monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer and sarcoma. Altogether, there were 47 patients with responses with a median duration of response of 75.7 weeks (range: 11.7+ to 85.9+ weeks, where "+" denotes censored value). The majority of these responses have been durable, with 72.3% (34/47) of responses ongoing as of the clinical cutoff date.

Analyses of tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results from Study PCD4989g suggest that PD-L1 expression in tumor-infiltrating immune cells is likely to be associated with response to ATEZOLIZUMAB.

Efficacy in Hematologic Malignancies

Eleven patients with hematologic malignancies have been treated with the anti PD-L1 antibody atezolizumab in the Phase Ia Study PCD4989g. This includes patients with refractory/late-line multiple myeloma (n = 4), FL (n = 3), cutaneous T-cell lymphoma (n = 2), DLBCL (n = 1), and Hodgkin's lymphoma (n = 1). Best responses of PR were observed in the 2 patients with cutaneous T-cell lymphoma, while best response of stable disease was observed in patients with FL (n = 3), Hodgkin's lymphoma (n = 1), and multiple myeloma (n = 2).

Additional patients have been treated with atezolizumab in the phase 1b study BO29563. This includes patients with relapsed/refractory follicular lymphoma and diffuse large B-cell lymphoma. Significant clinical activity has been observed among patients with follicular lymphoma, with an ORR of 21.4% (3/14) and CRR of 14.2% (2/14), plus 6 additional patients with stable disease

following cycle 4 (Palomba et al. 2016). For further details, see the ATEZOLIZUMAB Investigator's Brochure.

3.3.2.4 Clinical Pharmacokinetics

On the basis of available preliminary PK data (0.03 20 mg/kg), ATEZOLIZUMAB appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean clearance (CL) and the mean volume at steady state (V_{ss}) had a range of 3.20 4.43 mL/kg and 48.1 64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and AEs or IRRs has been observed.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

4.1.1 Rationale for Patient Population

This study is designed to obtain safety and efficacy data for atezolizumab and for atezolizumab plus low-dose, local radiotherapy in patients with relapsed/refractory follicular lymphoma. Enrollment will be offered to patients with relapsed/refractory follicular lymphoma who fulfill stringent eligibility criteria. This indication was selected in part because of preliminary evidence of activity of PD-1/PD-L1 antibodies in patients with follicular lymphoma. Patients will be randomly assigned to receive atezolizumab alone or atezolizumab plus low-dose, local radiotherapy (see Section 15). This study will allow an assessment of the activity of single-agent atezolizumab and of atezolizumab in combination with low-dose, local radiotherapy in patients with follicular lymphoma.

4.1.2 Rationale for Atezolizumab Starting Dose and Schedule

The dose of atezolizumab will be 1200 mg IV on Day 1 (+/-2 days) of each 21-day cycle.

The atezolizumab dose is informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg administered q3w. The MTD of atezolizumab was not reached and no DLTs have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03 20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg q3w, overall, atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies. Detectable ATAs were observed in patients at all dose levels but were only associated with changes in pharmacokinetics for patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower dose cohorts if administration of higher doses to patients with both detectable ATAs and reduced exposure would restore exposure to expected levels. No clear relationship between the development of measurable

ATAs and safety or efficacy has been observed. Available data suggest that development of detectable ATAs does not appear to have a significant impact on pharmacokinetics in most patients at doses of 10 to 20 mg/kg administered q3w. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg q3w dose levels have maintained target trough levels of drug despite the detection of ATAs.

Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q3w regimen (equivalent to the 1200-mg q3w fixed dose) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight. A fixed dose of 1200 mg q3w was selected (equivalent to a body weight based dose of 15 mg/kg q3w) on the basis of this analysis.

4.1.3 Rationale for Radiotherapy Dose and Schedule

In the FORT Trial, a phase III randomized non-inferiority trial comparing low-dose radiotherapy (4 Gy in 2 fractions) and conventional dose radiotherapy (24 Gy in 12 fractions) in patients with follicular lymphoma or marginal zone lymphoma having local radiotherapy for definitive or palliative local control, low-dose radiotherapy (4Gy in 2 fractions) was associated with minimal toxicity and high rates of local tumor control (44.3% CR, 29.8% PR).[4] In patients treated with an intratumoral TLR9 agonist, induction of circulating tumor reactive CTLs and responses at distant sites was only observed with concurrent low-dose, local radiotherapy with 4Gy in 2 fractions.[5] This dose and fractionation is therefore safe and sufficient to induce both local disease control and a systemic immune response in patients with follicular lymphoma.

4.1.4 Rationale for Potential Treatment Beyond Progression

Cancer immunotherapy may result in early apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions followed by delayed response (Wolchok et al. 2009). Additionally, responding tumors may appear to increase in size because of the influx of immune cells (Hoos et al. 2010; Pennock et al. 2012). Unconventional response patterns have been described in patients treated with anti-CTLA-4 (Wolchok et al. 2009) and have been observed in the preliminary experience with atezolizumab in Study PCD4989g. This has led to the use of Modified RECIST criteria to account for potential pseudoprogression in clinical trials of MPLD3280A. Patients with CLL and NHL treated with the Bruton tyrosine kinase inhibitor ibrutinib or the PI3K inhibitor idelalisib have demonstrated reduction in adenopathy and clinical responses accompanied by transient lymphocytosis (Davis and Letai 2012; de Rooij et al. 2012; Fiorcari et al. 2013). Tumor flare in patients with lymphoma and CLL has been described in patients treated with lenalidomide (Eve and Rule 2010; Chanan-Khan et al. 2011). This clinical response has been studied in vitro and is believed to be due to inhibition of B-cell receptor signaling and integrin

α4β1 adhesion of malignant cells to fibronectin and VCAM-1. Current response criteria for lymphoma do not take into account such lymphocytosis, which is a phenomenon somewhat similar to the pseudoprogression described above in solid tumor patients. The potential for false-positive results on PET scans are also observed for patients with lymphoma.

4.2 Intervention

All patients will receive open-label atezolizumab 1200mg IV on day 1 (+/- 2 days) of a 21-day cycle for 1 year, for a planned total of up to 17 cycles of therapy. For patients assigned to receive atezolizumab and low-dose radiotherapy, 4Gy will be administered in 2 fractions to a single nodal site amenable to radiation as identified by the radiation oncologist on day 2 and day 3 of Cycle 1.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Study Drug: ATEZOLIZUMAB

Once marketing authorization is received commercial ATEZOLIZUMAB will be used and will not be provided by Genentech for “on-label” studies. For studies done before marketing authorization and/or "out of label", ATEZOLIZUMAB will be provided free of charge by Genentech but switched to commercial drug once marketing authorization is received. Genentech will replace any ATEZOLIZUMAB drug that is not reimbursed. For studies done “out of label,” ATEZOLIZUMAB will be provided free of charge by Genentech. The Principal Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Genentech requirements.

5.1.1 Formulation

The ATEZOLIZUMAB drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of ATEZOLIZUMAB solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The ATEZOLIZUMAB drug product is formulated as 60 mg/mL ATEZOLIZUMAB in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

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.

5.1.2 Dosage Administration, and Storage

The dose level of ATEZOLIZUMAB to be tested in this study is 1200 mg (equivalent to an average body weight based dose of 15 mg/kg) administered by IV infusion every 3 weeks (every 21 [±2] days) for a total of 17 cycles. 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. Vital signs should be collected within 60 minutes prior to each infusion and at the end of each 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.

Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided in Section 9.2 and Section 11.2.1, respectively.

5.2 Low- Dose, Local Radiotherapy

5.2.1 Simulation

Simulation techniques may vary based on the location of the site that needs to be treated. PET or CT simulation will be done as per radiation oncologist discretion.

Simulation should be done prior to radiation treatment start.

Typically, patients will be positioned in an immobilization device, which may vary depending on the site that needs to be treated. An Alpha Cradle, Aquaplast mold, facemask, or equivalent immobilization devices may be used. Alternatively, simulation can be done without the use of any immobilization at the discretion of the treating radiation oncologist.

IV and oral contrast may be used for simulation, unless the patient has an allergy that cannot be adequately pre-medicated.

Motion management, including but not limited to deep inspiration breath hold and 4D scans, can be used at the discretion of the treating radiation oncologist.

5.2.2 Treatment Planning

When available, an FDG-PET scan is preferred for treatment planning purposes and will be acquired on a flat tabletop when possible with the same immobilization devices used for the treatment planning CT simulation. MRI scans may also be acquired when deemed necessary by the treating radiation oncologist.

A 3D conventional radiotherapy (3D CRT) or intensity-modulated radiation treatment (IMRT) plan will be developed using Eclipse TM. Institutional standards for radiation quality assurance and radiation delivery will be used.

Either photons or electrons can be used at the discretion of the treating radiation oncologist.

The concept of ISRT (involved-site radiotherapy) as discussed in more detail in the ILROG guidelines will be used [4].

Modern RT planning in lymphoma incorporates the current concepts of volume determination as outlined in the ICRU Report 83 [5] based on defining a gross tumor volume (GTV) and clinical target volume (CTV) which is expanded to create a planning target volume (PTV). The PTV is then used to define dose coverage. This approach allows direct comparison with the diagnostic imaging, increasing the accuracy with which lymph node localization is defined.

The gross tumor volume (GTV) will be identified on the treatment planning CT and PET-CT or MRI when used. The attending radiation oncologist after reviewing the diagnostic CT, and other available imaging modalities when available will define the final GTV.

CTV encompasses in principle the original GTV with a 1-2cm margin, even if extended beyond the involved tissue or organ. Yet, normal structures such as lungs, kidneys, muscles that were clearly uninvolved, though previously displaced by the GTV, should be excluded from the CTV based on clinical judgment. In outlining the CTV the following points should be considered

- Quality and accuracy of imaging
- Concerns of changes in volume since imaging
- Spread patterns of the disease
- Potential sub-clinical involvement
- Adjacent organs constraints

If motion management techniques are used, at sites where respiratory motion is involved an ITV (internal target volume) will be defined. ITV is defined in the ICRU Report 62 as the CTV plus a margin taking into account uncertainties in size, shape, and position of the CTV within the patient. The ITV is mostly relevant when the target is moving, most commonly in the chest and upper abdomen with respiratory movements.

PTV is the volume that takes into account the CTV (and ITV, when relevant) and also accounts for set-up uncertainties in patient positioning and alignment of the beams during

treatment planning and through all treatment sessions. Typically, the expansion from CTV (or ITV when used) is 0.5cm.

The clinician and / or treatment planner adds the PTV and applies margins that depend on estimated set up variations that are a function of immobilization device, body site, and internal organ motion and patient cooperation. In general, margins for uncertainties, which are based on probability levels, should be added quadratically in order to avoid overly large margins based on the most extreme and least likely situations.

The Organs at Risk (OAR) are critical normal structures that can manifest adverse effects from radiation, usually dependent on the radiation dose and thus can influence treatment planning or the prescribed dose. They should be outlined on the simulation study. The planner should calculate dose

Volume Histograms (DVH) and the plan should be evaluated by the clinician in consideration of this information.

- Institutional dose-constraints guidelines will be met.

5.2.3 Treatment Delivery (LINAC- based)

All patients will receive a total of 400cGy delivered in two fractions, one fraction per day, on days 2 and 3 of cycle 1.

Initial positioning will be based on the initial simulation parameters and will be based on KV imaging with shifts to bony anatomy as appropriate.

Active monitoring of treatment delivery accuracy will be accomplished using KV imaging immediately before all treatment fields.

5.2.4 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.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject 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

Relapsed or refractory follicular lymphoma grade 1, 2, or 3A

- Relapsed disease is defined as having relapsed after greater than 6 months of prior treatment for follicular lymphoma
- Refractory disease is defined as failure to achieve a complete response or relapsed within 6 months of treatment for follicular lymphoma

Pretreatment biopsy for fresh tumor tissue collection is required

- If patient has recently undergone a biopsy and has not received any intercurrent anti-lymphoma therapy, archival tissue can be used

Stage III/IV disease

- Stage II disease is also eligible if disease is not encompassible within a single radiation field, as determined by the radiation oncologist.

At least one prior treatment for follicular lymphoma (no restriction to number or type of prior therapies)

- Patients treated for transformed diffuse large B cell lymphoma (DLBCL) who have retrograde transformation are eligible provided they have received at least one prior treatment for the follicular lymphoma

Site of disease amenable to low-dose, local radiotherapy (2 x 2Gy), as recommended by the radiation oncologist.

At least one bi-dimensionally measurable lesion > *1.5* cm in its *longest diameter* by CT scan or magnetic resonance imaging as defined by *the Lugano Classification*

Adequate hematologic and end organ function:

- ANC ≥ 1500 cells/μL
  - If there is documented bone marrow involvement of follicular lymphoma, ANC must be ≥ 1000 cells/μL
- Platelet count ≥ 75,000/μL
  - If there is documented bone marrow involvement of follicular lymphoma, platelet count must be ≥ 50,000/μL
- Hemoglobin ≥ 9.0 g/dL
  - If there is documented bone marrow involvement of follicular lymphoma, hemoglobin must be ≥ 8.0 g/dL
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
  - Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.

- AST and ALT ≤ 3.0 × ULN
  - Patients with liver involvement: AST and/or ALT ≤ 5 × ULN
- Alkaline phosphatase ≤ 3 × ULN
  - Patients with documented liver involvement or bone metastases: alkaline phosphatase ≤ 5 × ULN
- Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 30 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
  - (140 age) × (weight in kg) × (0.85 if female)
    72 × (serum creatinine in mg/dL)

For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly) and to continue its use for 5 months after the last dose of ATEZOLIZUMAB. Women must refrain from donating eggs during this same period.

- A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

Willingness to undergo on-treatment biopsies unless not clinically feasible while on treatment

6.2 Subject Exclusion Criteria

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

General Exclusion Criteria:

Follicular lymphoma grade 3B

Concurrent aggressive non-Hodgkin lymphoma (eg, diffuse large B cell lymphoma [DLBCL])

Any anticancer therapy, including chemotherapy, hormonal therapy, investigational therapy, or radiotherapy, within 3 weeks, or 5 half lifes, whichever is shortest, prior to initiation of study treatment. However, the following are allowed:

- Hormone-replacement therapy or oral contraceptives
- Herbal therapy, provided it is discontinued at least 1 week prior to Cycle 1, Day 1
- Palliative radiotherapy for bone metastases, provided most recent fraction not given within 2 weeks of Cycle 1, Day 1 and most recent fraction was not administered to planned area of radiation while on study.

AEs from prior anticancer therapy that have not resolved to Grade $\leq$ 1, with exception of alopecia or skin/nail hyperpigmentation.

Bisphosphonate therapy for symptomatic hypercalcemia within 2 weeks of cycle 1, day 1

- Use of bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) is allowed. Denosumab should not be used while on therapy (see section 9.2.2)

Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease

Active central nervous system (CNS) involvement of lymphoma.

- Patients with a history of CNS involvement of lymphoma are eligible, provided they received treatment greater than 30 days prior to cycle 1 day 1 and there is no evidence of involvement on most recent assessment.

Pregnant or breastfeeding, or intention of becoming pregnant during study treatment or within 5 month after the final dose of study treatment.

- Women of childbearing potential must have a negative serum pregnancy test result within 30 days prior to initiation of study treatment.

Known hypersensitivity to Chinese hamster ovary cell products, other recombinant human antibodies, or to any component of the atezolizumab formulation.

Inability to comply with study and follow-up procedures

Active or history of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, 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 inactive inflammatory bowel disease, not currently receiving therapy, may be eligible.

- Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    - 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 is permitted provided patient is asymptomatic and did not require systemic or inhaled corticosteroids for treatment of symptomatic radiation pneumonitis.

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 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

Major surgical procedure within 28 days prior to Cycle 1, Day 1 or 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, within 5 months after the final dose, 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.

Malignancies other than the disease under study within 3 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.)

Medication Related Exclusion Criteria

Prior treatment with anti PD-1, or anti PD-L1 therapeutic antibody or pathway-targeting agents. Patients who have received prior treatment with anti CTLA-4 may be enrolled, provided the following reqirements are met:

- Minimum of 12 weeks from the first dose of anti CTLA-4 and > 6 weeks from the last dose
- No history of severe immune-related adverse effects from anti CTLA-4 (NCI CTCAE Grade 3 and 4)

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 1 week 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 or prednisone for intravenous contrast allergy) may be enrolled.
- Palliative systemic steroids for palliation of disease are allowed but must be discontinued at least 7 days prior to cycle 1, day 1
- 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

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. If the investigator is a member of the treatment team s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Furthermore, eligible patients from the lymphoma services will be identified by investigators at the time of medical disciplinary rounds or in clinic at Memorial Sloan Kettering Cancer Center.

8.0 PRETREATMENT EVALUATION

Pretreatment evaluations will be performed according to study flowchart in Appendix 1.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Atezolizumab administration

Atezolizumab will be administered on an every 21-day (+/-2 days) dosing schedule. Atezolizumab will be initiated at 1200mg IV for a planned total of 17 cycles of therapy. Dose modification or treatment interruption/discontinuation may occur as described in section 9.2.

For patients assigned to receive atezolizumab and low-dose radiotherapy, 4Gy will be administered in 2 fractions, on days 2 and 3 of cycle 1, to a single nodal site amenable to radiation as identified by the radiation oncologist (see section 5.2).

9.2 Concomitant and Excluded Therapies

9.2.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 14 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 Con TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with ATEZOLIZUMAB but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. 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 (see Section 6.2) should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

9.2.2 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:

- G-CSF solely to maintain the ANC and not associated with the treatment of a documented or suspected infection in the setting of febrile neutropenia
- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy
- Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions (DDIs) that may cause or confound assessment of toxicity.

The following therapies are excluded while patients are receiving atezolizumab and for 10 weeks after the last dose of atezolizumab:

- Patients who are receiving a RANKL inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead; denosumab could potentially alter the activity and the safety of atezolizumab.
- Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

- Patients should not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, and methotrexate. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti TNF 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.
- 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. Inactivated vaccines are allowed.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

9.3 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

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 13.1.

There will be no dose reduction for ATEZOLIZUMAB in this study. Patients may temporarily suspend study treatment for up to 42 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 > 42 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 10.2 and 10.3.

If a patient must be tapered off steroids used to treat AEs, ATEZOLIZUMAB may be held for additional time beyond 42days 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 the 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 other immunosuppressive agents.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to ATEZOLIZUMAB occurs at any time during the study, treatment with ATEZOLIZUMAB should be discontinued.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 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.

10.1 Laboratory/ Pathology 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 on site. Refer to section 12.2 and Appendix 9 for correlative studies workflow.

The following assessments will be performed at Memorial Sloan-Kettering Cancer Center:

Baseline tumor biopsy

- All patients will undergo a baseline tumor biopsy sample collection within 30 days of registration.
    - If the patient has recently undergone a biopsy and has not received any intercurrent anti-lymphoma therapy, archival tissue can be used

- Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
- Every intention should be made to collect the pre treatment biopsy from the same site that will be radiated. The on protocol biopsy should be in the same location unless clinically unfeasible or not in the interest of the patient's safety.

On-treatment tumor biopsy

- All patients will undergo an on-treatment tumor biopsy sample collection, if clinically feasible, during Cycle 2 (as per study flowchart in Appendix 1).
- Acceptable samples include fine needle aspirations or core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Core needle biopsies are preferred.
- The tissue will be used for correlative investigations.

Tumor biopsy at the time of initial radiographic progression (This tumor biopsy is **optional** based on whether it is feasible to obtain enough tissue at the site and therefore, 'clinically indicated/feasible', and not optional for the patient to choose whether or not they want one for the study)

- Patients may undergo a tumor biopsy sample collection, if clinically feasible, at the first evidence of early radiographic disease progression (i.e., not preceded by meaningful tumor regression). Biopsy at time of initial radiographic progression is recommended but not mandatory.
- Acceptable samples include fine needle aspirations or core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
- If CT-guided is necessary for the investigational on-treatment biopsy, the average tissue radiation dose resulting from CT-guided biopsy procedures is 4.56 mGy.

10.2 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.

10.3 Follow-Up Assessments

Patients who discontinue early from treatment or who complete the study treatment period will be followed as outlined below. If disease progression is clinically suspected, this should be confirmed by radiological examination as soon as possible. For patients who are being treated beyond progression, see Appendix 4 for the frequency of imaging assessments to monitor response.

10.4 Post-Treatment Evaluations

Patients who discontinue study treatment for reasons other than PD (e.g., toxicity) should continue to undergo the full tumor assessment 6 8 weeks after study treatment is discontinued and

every six months thereafter until the patient dies, experiences PD, withdraws consent, or until the study closes, whichever occurs first. Patients who start a new anticancer therapy in the absence of PD should continue to be followed for progression according to the protocol schedule unless consent is withdrawn, the patient dies, or the study closes, whichever occurs first.

For patients who experience PD or who discontinue the study treatment due to an AE or SAE, full tumor assessment should be obtained within 30 days after the last dose of study treatment or before another anticancer therapy is initiated. Additional required tests for these patients are outlined in Appendix 1.

Patients that drop out prior to evaluation due to PD, AE, SAE will be assessed for survival and toxicity every 3 months until the start of new anti-lymphoma therapy.

Female patients of reproductive potential who are not surgically sterile must practice adequate birth control for a minimum of twelve months post-treatment; male patients who are not surgically sterile must practice adequate birth control for a minimum of three months post-treatment.

10.5 Survival and Subsequent Anticancer Therapy

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the funding source of Principal Investigator. All patients who have discontinued treatment without disease progression will undergo all follow-up exams noted in Appendix 1 during follow-up. All other patients will be followed for survival and new anticancer therapy information only, unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

10.6 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 (i.e., efficacy analysis) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 2 years after the last patient is enrolled.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Definition of Adverse Event

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.

An adverse event is considered serious if it:

Results in death
Is life-threatening
Results in inpatient hospitalization of over 24 hours or prolongation of existing hospitalization
Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
Results in a congenital anomaly/birth defect
Is an Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Hospital admission for a planned procedure/disease treatment is not considered an SAE.

11.1.1 Adverse Events

All AEs (including SAEs and protocol-defined events of special interest [see Section 6.2]), regardless of attribution, will be recorded until 30 days after the last dose of study treatment, until study discontinuation/termination, or until initiation of subsequent anticancer therapy, whichever occurs first. After this period, investigators should report only those AEs (including pregnancy-related AEs) considered related to prior study treatment. Ongoing AEs considered related to study treatment will be followed until one of the following conditions is met: 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 it has been determined that study treatment or participation is not the cause of the AE.

See the Schedule of Assessments provided in Appendix 1for specified follow-up assessments.

11.1.2 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 MDPL3280A, 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 MDPL3280A; and/or the AE abates or resolves upon discontinuation of MDPL3280A or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than MDPL3280A (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.

11.1.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP. AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

The following AEs are considered of special interest and must be reported to the Genentech Drug Safety expeditiously (see Section 17.2 for reporting instructions), irrespective of regulatory seriousness criteria:

Adverse events of special interest for this study include the following:

Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
Treatment-emergent ALT or AST > 3xULN in combination with total bilirubin > 2xULN
Treatment-emergent ALT or AST > 3xULN in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Pneumonitis

Colitis

Endocrinopathies: Diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis

Hepatitis, including AST or ALT > 10xULN

Systemic lupus erythematsus (SLE)

Guillain-Barré syndrome

Myasthenia gravis or myasthenic syndrome

Meningoencephalitis

Nephritis

Myositis

Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
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)

Events suggestive of hypersensitivity, cytokine release, influenza like illness, systemic inflammatory response syndrome, SIA(systemic immune activation) or infusion reaction syndromes

11.1.4 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. adequately to Genentech Drug Safety during the follow-up period.

11.1.5 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. For more information, refer to Section 17.2.

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points 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?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. (See Section 11.3-11.7)

Exchange OF SINGLE CASE REPORTS

Memorial Sloan Kettering (MSK) will be responsible for collecting all protocol-defined Adverse Events (AEs) and Special Situation Reports (including pregnancy reports) originating from the Study for the Product.

Investigators must report all Adverse Events/Serious Adverse events (SAEs), AEs of Special Interest (AESIs) and Special Situation Reports (including pregnancy reports) adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed immediately upon completion to Genentech Drug Safety at:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MEDWATCH 3500A REPORTING GUIDELINES

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

Protocol description (and number, if assigned)

Description of event, severity, treatment, and outcome if known

Supportive laboratory results and diagnostics

Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

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

Adding to the original MedWatch 3500A report and submitting it as follow-up

Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

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

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/downloads/AboutFDA/ReportsManualsFo rms/Forms/UCM048334.pdf

Reporting to Regulatory Authorities, Ethics Committees and Investigators

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

Sponsor will be responsible for the distribution of safety information to its own investigators, where relevant

Additional Reporting Requirements for IND Holders (if applicable):

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR §600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of atezolizumab. An unexpected adverse event is one that is not already described in the atezolizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech/Roche within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of atezolizumab. An unexpected adverse event is one that is not already described in the atezolizumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR

§ 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech/Roche, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

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

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

And Sponsor will be responsible for the distribution of safety information to Site IRB

Tel: (212) 639-7592

Fax: (212) 888-0940

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

Tel: (888) 835-2555

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

AGGREGATE REPORTS

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

Sponsor will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

QUERIES

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

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

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. *Sponsor* agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche

11.2 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. AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, myositis, and myasthenia gravis, have been observed in Study PCD4989g. Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010).

A more detailed safety profile of ATEZOLIZUMAB is provided in the ATEZOLIZUMAB Investigator's Brochure.

11.2.1. Management of Specific Safety Concerns with ATEZOLIZUMAB

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions or systemic immune activation. Adverse events with potentially immune-related causes, including rash, hypothyroidism, hepatitis or elevated transaminase, colitis, myositis, and myasthenia gravis have been observed in Study PCD4989g.

For further details regarding clinical safety and a more comprehensive list of observed adverse events with atezolizumab, see the Atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al., 2010). Suggested workup and management guidelines for suspected immune-mediated adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

11.2.2 Management of Patients Who Experience Atezolizumab Specific Adverse Events

Guidelines for management of specific adverse events listed below are outlined in the Atezolizumab Investigator's Brochure.

Gastrointestinal toxicity

Hepatotoxicity

Dermatologic toxicity

Endocrine toxicity

Pulmonary toxicity

Potential pancreatic toxicity

Potential ocular toxicity

Neurologic toxicity

Immune-related nephritis

Immune-related myositis

11.2.3 Management of Systemic Immune Activation

Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents. SIA 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 SIA is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

Diagnostic criteria and recommended management of SIA is described in the table below (Table 2).

Table 2. Diagnostic Criteria and Management for Systemic Immune Activation

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
• Fever ≥ 38.5°C on more than one occasion • Ferritin ≥ 3000 ng/mL • Cytopenias (Grade ≥ 2 in two or more lineages) • Age-adjusted soluble IL-2 receptor elevated by ≥ 2 standard deviations • Severe dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated GGT or LFTs (AST, ALT, or total bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥ 4 major criteria	Consistent with SIA	• Permanently discontinue atezolizumab. • Consider treatment with an immunosuppressive agent (i.e., tocilizumab, infliximab, cyclosporine A, or etoposide) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent). • Contact the Medical Monitor for additional recommendations. • Consider HLH-94 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable SIA	• Depending on clinical severity, follow guidelines for "Consistent with SIA" or "Possible SIA" diagnosis. • The Medical Monitor may be contacted for recommendations.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible SIA	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • The Medical Monitor may be contacted for additional recommendations. • Follow guidelines for "Consistent with SIA" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.

11.2.4 Infusion Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., infusion related reaction) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF.

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.

For anaphylaxis precautions, see Appendix 7.

11.2.5 Safety Reconciliation

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

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

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

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

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

11.3 Diagnosis Versus Signs and Symptoms

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF 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, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

11.4 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 17.2), 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 17.2) that are attributed by the investigator solely to progression of disease should be recorded only in the study {e}CRF.

11.5 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”).

11.6 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.

11.6.1 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 within 5 Months after the last dose of study drug. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via fax. A pregnancy report will automatically be generated and sent to Genentech Drug Safety. Pregnancy should not be recorded on the Adverse Event CRF. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE 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.

A Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Genentech Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators")

11.6.2 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.

ATEZOLIZUMAB Male patients who received study treatment should not attempt to father a child until end of study. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and faxed to Genentech Drug Safety.

11.6.3 Abortions

Any spontaneous abortion should be classified as an SAE (as the Principal Investigator considers spontaneous abortions to be medically significant events), recorded on the Adverse Event CRF, and reported to Genentech Drug Safety immediately (i.e., no more than 24 hours after learning of the event; see Section 17.2).

11.6.4 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, and reported to Genentech Drug Safety immediately (i.e., no more than 24 hours after learning of the event; see Section 17.2).

11.7 Serious Adverse Events

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in 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
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

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

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

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Tumor and Response Evaluation

Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Irradiated sites of disease, previously irradiated lesions, or lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions. Response will be assessed by the investigator per the *Lugano Classification* (Cheson et al, 2014; see Appendix 4) at tumor assessment timepoints (see Appendix 5).

Site of disease deemed amenable to low-dose, local radiotherapy (2 x 2Gy) should not be counted as target lesions.

Previously irradiated lesions should not be counted as target lesions.

Lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions.

Bone lesions should not be counted as target lesions.

12.1.1 Outcome Measures

Response will be assessed by the investigator using the *Lugano Classification* (see Appendix 4).

12.1.2 Primary Efficacy Outcome Measure

Objective response rate of atezolizumab alone and of atezolizumab with low-dose, local radiotherapy (objective response defined as CR or PR; as measured in non-irradiated sites of disease).

12.1.3 Secondary Efficacy Outcome Measure

Progression-free survival and overall survival of atezolizumab alone and of atezolizumab with low-dose, local radiotherapy (as measured in non-irradiated sites of disease).

12.1.4 Safety Outcome Measure

Nature, frequency, severity, and timing of adverse events.

12.2 Correlative Studies

12.2.1 Assessment of T- Cell Receptor Diversity/ Clonality

We will determine if clinical responses to atezolizumab are associated with preexisting tumor antigen restricted effector T cells or the development of a more clonal T-cell receptor (TCR) repertoire, and we will determine what impact the addition of concurrent local, low-dose radiotherapy has on TCR diversity and clinical responses.

TCR clonality evaluation: Flow-cytometry-sorted CD4+ and CD8+ T cells from both pre and on-treatment biopsies and peripheral blood mononuclear cells will be separated and DNA will be promptly extracted using a low-input DNA extraction kit (Qiagen). Clonal TCR diversity will be assessed using the Adaptive ImmunoSEQ kit. The resulting multiplexed PCR product will be sequenced on an Illumina MiSeq system and analyzed using the ImmunoSEQ analyzer. (Appendix 9)

12.2.2 Assessment of Biomarkers Related to PD-L1, Tumor Biology, and Immune Cell Biology

Using immunohistochemistry, multiplex immunofluorescence, and fresh tissue immunophenotyping, we will assess biomarkers related to PD-L1 and/or immune cell biology and tumor biology that might contribute to our understanding of the mechanism of response to PD-L1 therapy and of the abscopal effect of radiation therapy in follicular lymphoma.

Immunohistochemistry of pre-treatment patient biopsies: Three to four (3-4) core biopsies will be fixed in formalin and allocated to the Molecular Cytology Core Facility for morphologic review and

immunohistochemistry (IHC). Immunohistochemical staining will be performed with antibodies against CD3, CD4, CD8, CD68, FoxP3, TBET, GATA3, B2M, MHC-I, MHC-II, PD-1, PD-L1, and PD-L2. We will follow previously well-established protocols for IHC analysis of FFPE tissue. (Appendix 9)

Flow cytometry analysis and sorting of pre and on-treatment patient biopsies Four (4) core biopsies will be placed in RPMI media and sent to Pathology. They will then be delivered to the Cell Marker Lab, where single cell suspensions will be generated. Clinical flow cytometry using 3-laser BD-FACSCANTO-10 instrument (Becton Dickinson Immunocytometry Systems (BDIS)) and 9-10 color assays (Appendix 9) will be performed with specific emphasis on markers likely to be affected by treatment with atezolizumab, including:

Basic T-cell subsets: $CD3^+$ T cells and 2 subsets: $CD3^+CD4^+$ and $CD3^+CD8^+$.

Effector and memory subsets: defined by CD45RA, CD28, CD27, and CCR7

Regulatory T cells: defined by CD4, CD25, CD127, and CCR4.

Activation/exhaustion: defined by expression of PD-1, LAG-3, TIM-3, and CTLA-4

Preferred order of core biopsies to be obtained, media, and destination of sample:

Core	Media	Destination
1	Formalin	Pathology
2	RPMI	Pathology
3	Formalin	Pathology
4	RPMI	Pathology
5	Formalin	Pathology
6	RPMI	Pathology
7	RPMI	Pathology
8	Flash Frozen	CSP
9	Flash Frozen	CSP
10	Formalin	Pathology

Peripheral blood:

All patients will have four (4) additional tubes of blood drawn during screening and on treatment as per Appendix 1.

Two (2) Green Top tubes are to be drawn and sent to the HOTB lab for PBMC Storage.

One (1) Red Top Tube is to be drawn and sent to the HOTB lab for serum cytokines assay.

One (1) Purple top tube will be ordered for SOC clinical flow cytometry. The remainder of this tube is to be delivered to the Cell Marker lab for subsequent testing.

Refer to Appendix 9 for more information regarding workflow for bloods collections and delivery. Serum will be frozen and peripheral blood mononuclear cells will be viably cryopreserved for flow cytometric analysis of T cells subsets (as above). Peripheral blood samples will be stored in Zuckerman 2013 (HOTB). (Appendix 9)

Should inadequate number of core biopsy samples be obtained, the priority for allocation of core biopsy samples will be as follows: (1) IHC, (2) TCR clonality evaluation, (3) Flow cytometry analysis. (Appendix 9)

12.2.3 Cytokine/ Chemokine Levels

To understand the prevalence of circulating cytokines/chemokines and the impact they may have on the clinical activity and/or safety of atezolizumab treatment, a panel of cytokines and chemokines may be investigated by ELISA or other protein assay methods. Levels of soluble PD-L1 in peripheral blood may also be assessed. One SST tube will be drawn during screening and on treatment as per Appendix 1, and will be sent to Zuckerman 1419 for processing and storage. (Appendix 9)

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 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
- Patient non-compliance

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). However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced if they received any protocol treatment.

See Sections10.3, 10.4, and 10.5 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

13.2 Study Treatment Discontinuation

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

- Pregnancy
- Immune related adverse event that requires atezolizumab to be withheld for >42 days
- Disease progression

In case of CT findings suggestive of pseudoprogression in patients with persistent clinical benefit investigator should contact the principal investigator to discuss further patient management. Because of the present potential for tumor flares immunotherapies, which result in early apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions followed by delayed response (Wolchok et al. 2009), patients whose CT scans meet criteria for disease progression may continue to receive study treatment at the discretion of the principal investigator (1) if a moderate increase is seen in 1 lesion only or (2) if at least two the following criteria are met:

Absence of symptoms and signs, including worsening of laboratory values (e.g. increased LDH) that indicate unequivocal disease progression.

No declining ECOG performance status

Absence of tumor progression to critical anatomical sites (e.g. leptomeningeal disease) cannot be management protocol-allowed medical interventions

The primary reason for study treatment discontinuation should be documented on the appropriate CRF.

Patients with radiographic evidence of progression/ residual metabolically active disease who continue to receive study treatment will require the following:

- CT scan repeated 4-8 weeks later after documenting pseudoprogression
- If the CT scan shows persistent or further progression a tumor biopsy will be completed.

Patients who discontinue study treatment prematurely will not be replaced.

13.3 Study and Site Discontinuation

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

The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.

Patient enrollment is unsatisfactory.

Genentech will notify the investigator if Genentech decides to discontinue the study.

The Principal Investigator has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

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)

14.0 BIOSTATISTICS

14.1 Determination of Sample Size

To accomplish our primary objectives we will use a randomized parallel 2-arm 1-stage design. All patients will be randomly assigned to one of the two treatment arms, and each arm will be monitored and analyzed separately. For both arms, a 43% or higher response rate is considered promising, whereas a 20% or lower is considered not promising.

Novel therapies [e.g. bortezomib or lenalidomide] have single agent ORR of ~20% in relapsed/refractory FL [Goy 2005, Witzig 2009, Di Bella 2010] and are highly active in combination [e.g. when combined with the anti-CD20 monoclonal antibody rituximab]. These data suggest that excluding an ORR <20% while targeting an ORR >43% would be a conservative approach to evaluation of atezolizumab treatment effect as a single agent or in combination with low dose local radiotherapy in this population of patients with relapsed/refractory FL. To this end for each arm, a total of 25 patients will be accrued (once one arm reaches the enrollment goal of 25, randomization will stop and all the future patients will be automatically assigned to the other arm).

If 8 or fewer patients in either treatment arm respond, that treatment will be considered not promising. If 9 or more patients respond in either treatment arm, then that arm will be declared promising and worthy of further investigation.

This 1-stage design has type 1 and 2 error rates at 0.05 and 0.2, respectively. Given this design we may stop either arm early if we have observed 17 or more non-responders. If both arms are declared desirable by demonstrating 9 or more responses in their 25-patient cohorts, we will use the pick-the-winner approach as a general principle where the choice of which arm will be suitable for further study will be based on the absolute number of responses. If the treatment arm with a higher number of responses is also associated with more toxicity, then the investigators will weigh both the absolute number of responses and toxicity in selecting which arm is suitable for further study. If the difference in the true response rates of the treatment arms is 10% (i.e. 43% vs 53%) then the chance that the regimen with the higher response rate will be picked is over 70%. If the difference in the true response rates of the treatment arms is 15% (i.e. 43% vs 58%) then the chance that the regimen with the higher response rate will be picked is over 80%.

14.2 Planned Efficacy Evaluations

Patients will have their response classified according to the *Lugano Classification* as outlined in Appendix 4. Patients who have received at least one cycle of therapy and the planned radiation therapy (if randomized to receive radiotherapy) will be considered evaluable for response. Patients will be monitored periodically for the primary and secondary measurements (see Appendix 4 and Appendix 5 for protocol requirements regarding required imaging modalities and reporting requirements).

14.3 Primary Efficacy Variables

Objective response is defined as a CR or PR, as determined by investigator assessment using *the Lugano Classification* on *Treatment Response Assessment Timepoints* (Appendix 4). Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered nonresponders in the analysis of objective response.

14.4 Secondary Efficacy Variables

PFS is defined as the time from the first day of study treatment to PD or death, whichever occurs first. If a patient is alive and has not experienced PD, PFS will be independently censored at the day of the last tumor assessment. Patients with no post-baseline tumor assessments will be included in the PFS analysis but censored at the start of treatment.

OS is defined as the time from the first day of study treatment to death from any cause. For OS, patients without a date of death will be independently censored on the date a patient was last known to be alive.

Incidence of toxicity and adverse events will be summarized by frequencies and percentages for each of the two cohorts.

Patients with early withdrawal from the study will be considered as independently censored according to previous paragraphs. However, the censoring may be related to the disease status and therefore not independent. Therefore, sensitivity analyses will be conducted where these patients will be counted as events.

14.5 Method of Analysis

The best overall response is the best response recorded from the start of treatment until progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started), and is the best overall response rate at any response assessment timepoint (see Appendix 5). Objective response rates will be described for patients assigned to each treatment arm as long with exact 95% confidence intervals.

Progression-free survival, and overall survival will be calculated from the start of treatment by using the Kaplan-Meier method along with 95% confidence intervals. Patients' withdrawals from interventions for reasons other than progression or death will be treated as independent censoring, and sensitivity analyses will be conducted as described in 14.4

14.6 Method of Analysis for Correlative Endpoints

Objective response rates, progression-free survival, and overall survival will be estimated for patients with preexisting tumor antigen restricted tumor infiltrating lymphocytes (TILs) and patients without preexisting tumor antigen restricted (TILs), and for patients who demonstrate a 2-fold expansion of T cell receptor (TCR) clonality and patients who do not demonstrate a 2-fold expansion of TCR clonality, and groups will be compared using Fisher's exact tests (ORR) and logrank tests (PFS and OS). Similar comparison will be performed to associate other biomarkers described in 2.3

with the outcomes. To assess the impact of treatment on peripheral blood cytokine/chemokine levels, Wilcoxon signed rank test will be used to test the intra-patient changes in these factors.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

After eligibility is established and immediately after consent is obtained, patients will be registered and randomized. Patients will be randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block. At the time of registration, patients will be randomized to either receive radiation (GROUP 1) or to not receive radiation (GROUP 2).

16.0 DATA MANAGEMENT ISSUES

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accural rates and extent and accuracy of evaluations and follow- up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the Memorial Sloan Kettering Cancer Center IRB.

16.1.1 Data Entry and Database

The data will be collected and entered into electronic Case Report Forms (eCRFs) using the internet based system Medidata Rave.

	Required Medidata Forms			
	Baseline	**Visit**	**SAE**	**Off Study**
Screening Forms	X			

Visit Forms		X		X
Concomitant Medications Form	X	X	X	X
Adverse Event Forms		X	X	X
Treatment Forms		X		X
Laboratory Forms	X	X	X	X
Response Forms		X		X
Hospitalization Forms			X	
MSK SAE Report Form			X	
Off Study Forms				X

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at http://www.cancer.gov/clinicaltrials/conducting/dsm- guidelines. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.)Will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.2.1 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 90 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 (see Section 17.2) will be reported in an expedited fashion (see Section 17.2). 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.

16.2.2 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.

16.2.3 Management of Specific Safety Concerns with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions or systemic immune activation. Adverse events with potentially immune-related causes, including rash, hypothyroidism, hepatitis or elevated transaminase, colitis, myositis, and myasthenia gravis have been observed in Study PCD4989g.

For further details regarding clinical safety and a more comprehensive list of observed adverse events with atezolizumab, see the Atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al., 2010). Suggested workup and management guidelines for suspected immune-mediated adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

16.3 Retention of Records

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application

approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

16.4 Study Close-Out

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

ATEZOLIZUMAB Protocols

Email: anti-pdl-1-mpd3280a-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.1.1 Confidentiality

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

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

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

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

Death
A life-threatening adverse event
An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
Results in a congenital anomaly/birth defect
Is an Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

The date the adverse event occurred
The adverse event
The grade of the event
Relationship of the adverse event to the treatment(s)
If the AE was expected
Detailed text that includes the following
- An explanation of how the AE was handled
- A description of the participant's condition
- Indication if the participant remains on the study

If an amendment will need to be made to the protocol and/or consent form
If the SAE is an Unanticipated Problem

17.2.1 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the U.S. Food and Drug Administration (FDA),

appropriate Institutional Review Boards (IRBs), and Genentech, Inc., in accordance with CFR 312.32 (Investigational New Drug [IND] Safety Reports).

17.2.3 Adverse Event Reporting to Genentech

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), and other Special Situation Reports where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

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

SADRs

Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

Other SAEs

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

AESIs

AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Special Situation Reports

Pregnancy reports

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

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

Other Special Situation Reports

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

Data related to the Product usage during breastfeeding

Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)

Drug interaction

Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.It is understood and agreed that the Sponsor will perform adequate due diligence with regard to obtaining follow-up information on incomplete AE, Special Situations and pregnancy reports.

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

IND Annual Reports

Copies of all IND annual reports submitted to the FDA by the Principal Investigator should be sent to Genentech Drug Safety via fax:

Fax: (650) 225-4682 or (650) 225-5288

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their

inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

The nature and objectives, potential risks and benefits of the intended study.

The length of study and the likely follow-up required.

Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

The name of the investigator(s) responsible for the protocol.

The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

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20.0 APPENDICES

20.1. Appendix 1- Study Flowchart

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

20.3. Appendix 3- Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

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20.1 Appendix 1

Flowsheet

	Screening	Cycle 1	Low-dose radiotherapy	Cycle 2		Treatment Visits	Treatment Visits	Follow Up Visits	Off Treatment Visit
	within 30 days of C1D1 unless otherwise specified	Day 1	Cycle 1, Day 2 and 3	Day 1 (+/- 2 days)	Day 14-20	Cycle 3, 4, 6, 7, 8, 10, 11, 12, 14, 15, 16: Day 1 (+/- 2 days)	Cycle 5, 9, 13, 17: Day 1 (+/- 2 days)	Every 6 Months (+/- 14 days)	
Informed consent [L]	X								
Medical history and demographics	X								
Physical examination, including vital signs[a], height , weight, and performance status	X	X		X		X	X	X	X
Adverse events	X	X		X		X	X	X	X
Concomitant medications	X	X		X		X	X	X	X

Bone marrow biopsy & aspirate	X[d]			X[d]		X[d]	X[d]	X[d]	X[d]
CBC w/ differential [b]	X	X[j]		X[j]		X[j]	X[j]	X	X
Chemistry panel [c]	X	X[j]		X[j]		X[j]	X[j]	X	X
TSH[i]	X	X[j]		X[j]		X[j]	X[j]	X	X
Creatinine phosphokinase	X	X[j]		X[j]		X[j]	X[j]	X	X
PTT and PT/INR	X								
Urinalysis	X								
Infectious disease testing[k]	X								
Pregnancy test (urine or blood) [n]	X [n]								
Tumor Assessment	X[e]						X [em]	X[e]	X[e]
Tumor biopsy	X[f]				X[f]				X[f]
Research blood samples	X[g]				X[g]		X[g]	X[g]	X[g]

Radiation oncology consultation	X								
Low- dose radiotherapy[h]			X[h]						
Electrocardiogram	X								X

[a] Heart rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[b] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).

[c] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, uric acid, magnesium, phosphorus.

[d] Bone marrow biopsy and aspirate is required within 60 days of C1D1, provided no treatment has been administered in the interim. For patients with involvement of follicular lymphoma at baseline, repeat testing is required only to confirm CR or as clinically indicated.

[e] Imaging and reporting requirements for tumor assessment is described in Appendix 5. Patients will require a PET scan with diagnostic quality CT CAP (with intravenous and oral contrast, unless contraindicated) at study screening, Cycle 5, and EOT. A baseline PET with diagnostic CT CAP scan is required within 45 days of C1D1. For patients who have had a PET scan performed within 45 days of C1D1, a simulation scan (PET, CT, or MRI) will only be done if the patient is randomized to Arm 2 (RT arm). For patients who have not had a PET scan within 45 days of C1D1, baseline PET imaging will be a PET-simulation scan.

[f] Tumor biopsy is required in all patients within 45 days of C1D1. Tumor FNA or core biopsy is required in all patients at Cycle 2 Days 14-20 (core biopsy is preferred). Tumor biopsy is recommended at time of progression on study. Tumor biopsy should be outside the field of radiation to allow for an accurate assessment of systemic changes to the tumor microenvironment following local irradiation. Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions

[g] Research blood samples will be collected for correlative investigations as outlined in Section 12.2 of the protocol. Additional information about the workflow for correlatives can be found in Appendix 9.

[h] Only if randomized to low- dose radiotherapy arm

[i] T3 and T4 should be tested only if TSH is abnormal.

[j] Labs can be done within 5 days of day 1 of each cycle.

[k] Infectious disease testing includes: Epstein-Barr virus (EBV) serology (EBNA IgG), Hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), HCV serology (anti-HCV), and HIV 1 & 2 antibodies. HBV DNA test is required for patients who have positive serology for anti-HBc. HCV RNA test is required for patients who have positive serology for anti-HCV.

[L] Within 45 Days of C1D1

[m] On treatment imaging window must be +/- 14 days of Cycle X Day 1 target date.

[n] For women of childbearing potential

22.2 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.

22.3 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

22.4 Appendix 4

The Lugano Classification

Selection of Target Lesions[1]

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in two *diameters (longest diameter [LDi] and shortest diameter)*at baseline
   All nodal lesions must measure:
   1.5 cm in *LDi* regardless of short axis measurement.

2. All *measurable* extranodal lesions *should have an LDi* 1.0cm. *All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target lesions.*
3. If possible, the lesions should be from disparate regions of the body.
4. Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Selection of Nontarget Lesions[2]

Nontarget lesions will be qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions will be classified as nontarget lesions, including any measurable lesions that were not chosen as target lesions. Examples of nontarget lesions include:

1. All bone lesions, irrespective of the modality used to assess them
2. Lymphangitis of the skin or lung
3. Cystic lesions

Splenomegaly and hepatomegaly (all lymphomas)

The recommendation is to use a cutoff for splenomegaly of more than 13 cm. Similar to splenic involvement, diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver involvement.

4. Irradiated lesions
5. Measurable lesions beyond the maximum number of six
6. Groups of lesions that are small and numerous
7. Pleural/pericardial effusions and/or ascites
8. For this study, a significant increase in existing pleural effusions, ascites, or other fluid collections will be considered sufficient evidence of progression and will not require cytological proof of malignancy. Effusions, ascites or other fluid collections will be followed as non-target lesions.

---

[1] *Target Lesions are reported on the cCRF "Indicator Lesion" form.*

[2] *Nontarget Lesions are reported on the eCRF "Non-Indicator Lesion" form.*

Existing effusions/ascites: Effusions, ascites, or other fluid collections will be followed as nontarget lesions. At each time point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed. **New effusions/ascites:** Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions.

Response should be determined on the basis of radiographic and clinical evidence of disease. For the end-of-treatment response assessment, an FDG-PET will be performed *during*Cycle *10, between Days 15 and 21.* Assessment by PET should follow the criteria described by *Cheson et al. 2014*, which is presented in the table *below (the Lugano Classification)*.

Response and Site	PET-CT-Based Response	CT-Based Response
Complete Response	Complete metabolic response	
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on PET It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Complete radiologic response (all of the following): • Target nodes/nodal masses must regress to ≤1.5 cm in LDi • No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC-negative
Partial Response	Partial metabolic response	Partial remission (all of the following): • ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value • When no longer visible, 0 × 0 mm • For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation

Response and Site	PET-CT-Based Response	CT-Based Response
Lymph nodes and e<tralymphatic sites	Score 4 or S• wtih raducod uptak e compared ,.;th baseli ne and resi dual mass(es)of any size At interim, these findings suggest responding disease At end of treatment, these findingsIndicate rosldue disease	
Nonmeasuredlesions	Not applicable	AbsenVnormal. regressed.. but noincrase
Organ enlargement	Not applicable	Spleen must have regressed bY >50% inllength beyond nomal
New lesions	None	None
Bone rnarrCYtN	Residual uptake higher than uptake in normal **marrow but reduced compared with baseline** (diffuse uptake compatible with reactive changes trom chem otherapy allowed). If thole are persistent focalchanges in the matrow in tho context of a nodalresponse, consideration should be given to further evaluation 'hith MRI or biopsy or an Interval scan	Not applicable
No Response or Stable Disease	No metabolic response	Stable disease
Target ncdcs/ncdal masses, cxtranodal **lesions**	**Score 4 or 5 with no significant change in** FOG uptake from baseline at interim or end of treatment	**<50% decrease from bascfinc in SPD of up to** 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasumd lesions	Not applicable	**No increase consistent with progression**
Organ enlargement	Not applicable	**No increase consistent \with progression**
New lesions	None	None
Bone marrow	No change from baseline	Not appllcable

and Site	PET-CT-Based	CT-Based Response
Progmssiu Diaaa	Pr<:>gnas!liw metabolic dis-e	Prog reuiw disease requl1"1!S at least one of the loliowinc PPD progl'li'lllllion:
lndhAdu!ll nooesInodal masses	Sc<lll!I 4 or 5 with IUi incmae in of bas >line	
E:.tranodallesiorrs	N!ilw FDG·a\lid 10ci c< Mis!Bnt with'"""""""""""" alinterim or end..of.treatm >nlassessment	An indi11idual nodelk!sion mu!lt be abnonnal with; • LOI >1.5 em and • Increase ;,;50% fronn PPD nedir and • An increase in LOI or SDi f10m nadir • 0.5 em lbr lmloM ,;2 em • 1.0 em lbr lmloM >2 em • In tne settiog ot , 1he sphmk: length must increase by >50% ot lhe extent of its prior Increase baseline a 15om sp i!l!l'l muslioo ease to 16 If no splen<)ml!gl!ly, must inc ease bv alleasl2 em hm bas!l4iıı!!
Nonmeasured iesiorrs	None	• New or recurrent spl•oom New or clear of pre,existirlg oonmeasured lesiOns
New Lesions	New FDG·e\lid fi:lci c< Mlstent wlth lYnlph,orrJa rather than another alilliOSlY (e.g., infection, lnlaJnmallion). If uncE>llaln nega1rding!!llotogy of new hi"""""or interval scan may be coooidered	• of resolved lesiorrs • A new node > 1,5 em in any axis • A new axtrenodalsite >1 .0 em in any i! 1.0 em in any its pl"l!Sence must be uneaulvocaland must be allribcmble to ymphoma • Al>ses!lable disease of size uno qtli'llO>eallly attributable to
Bone Merrow	New or recurrent FDG-a11id fi:lci	New or recurrent inwlwment

5PS S.point scale; CT computed tomography; FOG luorodeoxyglucose; Gt gastrointestinal; IHC : mmunohistochemistry; LDi.longest transverse di ameter or a lesion; MRI magnetic resonance imag,ng; PET poSitron emission tomography: PPO cross product of Ihe LDi and perpendicular diameter: SOI shortest axis perpendicular to the LOI; SPO–sum of the product or the perpendicular diameters br multiple lesions.

- A score of 3 'n many patients indicates a good prognosis Wlth standard treatment, especially il at the lime of an 1nterim scan. ver , in trials on\Oivlng PET where de-escal allon Is Inl<IsIlgated, it may be pn;fetable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions : up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be cleay measurable in two diameters. Nodes should prelerably be from disparate regions of the body and should include, where applicable, mediastinal and retrope toneal areas. Non-nodal leslons Include those In sdid orga11s (e.g., llwr, spleen, kidneys, lungs). GI Involvement, cut.aooous lesions. or those noted on palpallon. Nonmoasurod lesions : any disease not solocted as measured, dominant disease and truly assessable disease should be considered not measured. These sites Include any nodes. nodal masses. and extranodal sites not sdected as dominant or measurable or that do not meet the requirements br measurebllity but are slll considered abnonnal, as well as truly assessable disease, whichls any site of suspected disease that would be difficult to bllow quantitatively with measurement, including pleural effusions, asc1tes, bone lesions, leptomeningeal disease, abdominaJ masses, and other lesions that cannot be confirmed and followed by imaging. In effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confinned and followed by 'maging. In Waldeye(s ring or in extranodal sites (e.g., Gl tract, ln.er, bone marrow), FOG uptake may be greater than 1n the mediastinum with complete metabolic response, but should be no higher than surrounding nonnal physiologic uptake (e.g., v.;th marrow activ tion as a result of chemolherapy or myeloid growth factors).
- PET SPS: 1, no uptake above background; 2, uptake s mediastinum: 3. uptake > mediastinum but Sliver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

22.5 Appendix 5
Imaging and Reporting Requirements for Tumor Response Assessments

Imaging and Reporting Requirements for Tumor Response Assessments

Timepoint	Imaging Modality	Reporting Requirement
Screening (within six weeks of C1D1)	PET-CT (must include diagnostic quality CT scan)	NA
On Treatment Response Assessment C5D1	PET-CT (must include diagnostic quality CT scan)	PET-CT criteria and CT critera
On Treatment Response Assessments (C9D1, C13D1, +/- 14 days)	CT only	CT criteria
End of Treatment (4-6 weeks after C16)	PET-CT (must include diagnostic quality CT scan)	PET-CT criteria and CT critera
Follow-up (every 6 months, +/- 4 weeks)	CT only	CT criteria

C =cycle; D = day; CT = computed tomography; NA = not applicable; PET-CT = positron emission tomography-computed tomography.

All response criteria (PET-CT and CT) are based on the 2014 Lugano Classification (see Appendix 4).

If the response assessment is discordant between the PET-CT and CT-based response, a follow-up scan in 2-3 weeks (prior to the next cycle of therapy) is recommended to determine response (see the study schema [Figure 1]).

For patients who are being treated beyond progression, CT scans (PET is optional) should be preformed every 3 months as long as treatment is ongoing and 4-6 weeks after the last dose of atezolizumab. Thereafter, patients will undergo CT scans every 6 months.

22.6 Appendix 6
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, th following procedures should be performed:

1. Stop the study drug infusion.
2. Aplly 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.

22. 7 Appendix 7
Safety Reporting Fax Cover Sheet

Genentech
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GENENTECH SUPPORTED RESEARCH

AE/SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

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 FDA MEDWATCH 3500 Form or SAFETY REPORT BEHIND THIS COVER SHEET.

22. 8 Appendix 8

Management Of Toxicities Associated With Atezolizumab

To date, the following adverse events are identified risks associated with atezolizumab: dermatologic reactions, hepatitis, hypothyroidism, pneumonitis, influenza-like illness, and IRRs. Potential risks associated with atezolizumab include colitis, endocrine disorders, hypersensitivity, neurologic disorders, pericardial effusions, eye toxicity, and development of anti-therapeutic antibodies. Detailed information is provided below for the following risks: GI toxicity, hepatotoxicity, dermatologic toxicity, hypothyroidism, pulmonary toxicity, influenza-like illness, systemic immune activation (SIA), pancreatic toxicity, pericardial effusions, eye toxicity, and IRRs.

Gastrointestinal Toxicity

Immune-related colitis has been associated with the administration of atezolizumab and is an identified risk for atezolizumab.

Patients should be advised to inform the investigator if any event of diarrhea occurs, even if it is mild. Suspected colitis should be further evaluated, and infectious or alternative etiologies should be ruled out.

If the event is of significant duration (>5 days) or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein or platelet count or bandemia), it is recommended to do the following:

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 diagnosis of colitis. If possible, one or two biopsy specimens should be snap frozen and stored.

Perform laboratory tests to rule out alternative etiology (i.e., WBCs and stool calprotectin).

Hepatotoxicity

Immune-related hepatitis has been associated with the administration of atezolizumab. Hepatitis is an identified risk for 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.

Patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have hepatic enzyme tests performed immediately, and results should be reviewed before administration of the next dose of study treatment.

If hepatic enzymes become elevated, neoplastic, concurrent medication, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for the hepatic enzyme elevations. Anti nuclear antibody, perinuclear anti neutrophil cytoplasmic antibody, anti liver kidney microsome antibodies, and anti smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Dermatologic Toxicity

Treatment-emergent rash has been associated with atezolizumab. The majority of the cases of rash were mild in severity and self-limited, with or without pruritus. Dermatologic reactions are an identified risk for atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Hypothyroidism

Hypothyroidism has been associated with the administration of atezolizumab and is an identified risk for atezolizumab. Patients with unexplained symptoms such as fatigue, myalgia, impotence, mental status change, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathy, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T4 levels should be evaluated to determine whether thyroid abnormalities are present. TSH, prolactin, and morning cortisol levels will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC. Pneumonitis is an identified risk for atezolizumab. Mild to moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension, as outlined below:

Measurement of oxygen saturation (i.e., arterial blood gas)
High-resolution CT scan of the chest
Bronchoscopy with bronchoalveolar lavage and biopsy
Pulmonary function tests (including diffusion capacity of the lung carbon monoxide)
Pulmonary function testing with a pulmonary embolism protocol

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Influenza-Like Illness

Influenza-like illness has been reported in patients receiving atezolizumab as a single agent and in combination with vemurafenib, bevacizumab, or platinum doublet therapy. Symptoms have included fever, fatigue, asthenia, chills, myalgia, arthralgia, and headache. Symptoms have occurred alone or concurrently. Influenza-like illness has been observed primarily 1-2 weeks after the first treatment cycle. The events have been mild to moderate in severity.

Systemic Immune Activation

SIA is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk. SIA should be included in the differential diagnosis for patients who develop a sepsis-like syndrome after administration of atezolizumab. Initial workup should include serum ferritin, CBC, liver function tests, serum triglycerides, and a coagulation profile. In the event of suspected SIA, the Medical Monitor should be contacted for additional recommendations. Treatment with agents such as tocilizumab, as well as corticosteroids, should be considered in the event of SIA.

Potential Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of other immunomodulatory agents.

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate assessments should include an evaluation for obstruction, as well as serum amylase and lipase tests. If immune-related pancreatic toxicity is suspected, IgG4 levels and auto-antibodies (anti-plasminogen-binding protein peptide antibodies, peripheral anti-neutrophil cytoplasmic antibodies, anti-mitochondrial antibody, anti-lactoferin antibody, anti-carbonic anhydrase II, anti-smooth muscle antibody, and anti-nuclear antibody) should be evaluated.

Pericardial Effusions

Pericardial involvement with associated effusions is common in patients with NSCLC and has the theoretical potential to be exacerbated by inflammation associated with anti-tumor immunity following PD-L1 blockade.

Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with preexisting pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial effusions, appropriate assessments include evaluations of cytology, LDH, glucose, cholesterol, and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstration of hemodynamic stability, and resolution of right ventricular dysfunction.

Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints by examination. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Patients in the study are encouraged to maintain eye hydration, generally through the use of moisturizing eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Infusion-Related Reactions

With single-agent atezolizumab, IRR symptoms during the infusion have included fever, chills, dyspnea, and flushing/hypotension. They may occur within 30 minutes to 24 hours after infusion, are generally mild and manageable, and wane with subsequent infusions. The most common symptoms reported within 24 hours of the first cycle were pyrexia, fatigue, nausea, hypertension, headache, and diarrhea. IRRs have been reported during Cycles 1 and 2.

Guidelines for Management of Toxicities

Event	Action To Be Taken
General guidance for treatment delays and discontinuation	• Permanently discontinue study treatment if any of the following events occur: – Grade ≥ 3 non–immune-related adverse event that is considered to be related to study treatment and does not resolve to Grade ≤ 2 within 21 days – Non–immune-related adverse event that is considered to be treatment related and requires study treatment to be withheld for > 21 days – Immune-related adverse event that requires atezolizumab to be withheld for > 42 days
IRRs and anaphylaxis	• Guidelines for the management of IRRs are provided above for atezolizumab. • In case of anaphylaxis, study treatment should be permanently discontinued.

CT=computed tomography; FL=follicular lymphoma; G-CSF=granulocyte colony-stimulating factor; IRR=infusion-related reaction; LMWH=low-molecular-weight heparin; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NHL = non-Hodgkin's lymphoma; NSAID=nonsteroidal anti-inflammatory drug; TLS=tumor lysis syndrome; TSH=thyroid-stimulating hormone; ULN=upper limit normal.

[a] Dose modifications apply only to events that are considered to be related to lenalidomide.

[b] According to Cairo-Bishop classification system.

[c] Graded according to NCI CTCAE Version 3.0.

Guidelines for Management of Toxicities (cont.)

Event	Action To Be Taken
AST, ALT, or bilirubin increase Grade 3 (or >10 x ULN for patients with liver involvement)	Withhold study treatment and monitor liver enzymes at least every 7 days. Investigate etiology Consult with a hepatologist if immune etiology is suspected. ▪ Corticosteroid treatment may be required for immune-related hepatitis ▪ If there is improvement to Grade ≤ 1, resume atezolizumab at full dose. Note: If hepatitis is treated with corticosteroids, atezolizumab should not be resumed until the corticosteroids have been tapered to ≤ 10 mg/day of prednisone or equivalent. ▪ Permanently discontinue study treatment for life-threatening liver toxicity
Amylase or lipase increase: Grade 3	▪ Withhold study treatment. Investigate etiology Consult with a gastroenterologist if immune etiology is suspected Corticosteroid treatment may be required for immune-related pancreatitis ▪ If there is improvement to Grade ≤ 1 and patient is asymptomatic, resume atezolizumab at full dose and resume lenalidomide at current dose. Note: If pancreatitis is treated with corticosteroids, atezolizumab should not be resumed until the corticosteroids have been tapered to ≤ 10 mg/day of prednisone or equivalent.
Ocular toxicity Grade 2 (autoimmune uveitis, iritis, or episcleritis)	▪ Withhold study treatment. ▪ Investigate etiology Consult with an ophthalmologist • If there is improvement to Grade ≤ 1, resume atezolizumab at full dose. ▪ For immune-related toxicity attributable to atezolizumab, start topical corticosteroid eye drops

CT=computed tomography; FL=follicular lymphoma; G-CSF=granulocyte colony-stimulating factor; IRR=infusion-related reaction; LMWH=low-molecular-weight heparin; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NHL = non-Hodgkin's lymphoma; NSAID=nonsteroidal anti-inflammatory drug; TLS=tumor lysis syndrome; TSH=thyroid-stimulating hormone; ULN=upper limit normal. • Dose modifications apply only to events that are considered to be related to lenalidomide.

[b] According to Cairo-Bishop classification system

[c] Graded according to NCI CTCAE Version 3.0.

E.ent		Action To Be Taken
Diarrhea	Grade 4	Pennanently discontinue study treatment. ▪ Corticosteroid treatment is suggested for colitis manifested as Grade 4 diarrhea.
	Grade 2 or 3	Withhold study treatment. Investigate etiology Consult with a gastroenterologist if immune etiology is suspected ▪ Corticosteroid treatment may be required for colitis manifested as Grade 3 diarrhea. If diarrhea improves to Grade :::1, resume obinutuzumab at full dose. ▪ If immune-related diarrhea improves to Grade :::1 and any colitis has cleared as confinned by sigmoidoscopy (or colonoscopy, if appropriate) with coloric biopsy, resume atezolizumab at full dose. Note: If colitis is treated with corticosteroids, atezolizumab should not be resumed until the corticosteroids have been tapered *to:::* 10 mg/day off prednisone or equivalent.
Pneumopathy, non-infectious (i.e., dyspnea, hypoxia, pulmonary infiltrates)		▪ Withhold study treatment. Investigate etiology Consult with a pulmonologist. ▪ If symptoms have resolved and CT lung findings are clear, resume atezolizumab at full dose.
Tumor flare reaction	Grade 3-4 [c]	▪ Withhold study treatment. Administer corticosteroids, NSAIDs, and/or narcotic analgesics at in.estigator's discretion. ▪ If there is improvement to Grade:::1, resume atezolizumab at full dose.
	Grade 1–2 [c]	Continue study treatment. ▪ Administer corticosteroids, NSAIDs, and/or narcotic analgesics at in.estigator's discretion.

CT=computed tomography; FL=follicular lymphoma; G-CSF=granulocyte colony-stimulating factor, IRR=infusion-related reaction; LMWH=low- molecular-weight heparin; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse E.ents; NHL = non-Hodgkin's lymphoma; NSAID=nonsteroidal anti-inflammatory drug; TLS=tumor lysis syndrome; TSH=thyroid-stimulating hormone; ULN=upper limit normal. • Dose modifications apply only to e.ents that are considered to be related to lenalidomide.

[b] According to cairo-Bishop classification system

[c] Graded according to NCI CTCAE Version 3.0.

22. 9 Appendix 9
Correlative Studies Work Flow

Pre-treatment, on-treatment and relapsed biopsies will undergo the same analysis/processing and storage, to be performed at three designated MSKCC sites (Pathology Core, Diagnostic Molecular Pathology [DMP] and Hematologic Oncology Tissue Bank [HOTB])

INTERVENTIONAL RADIOLOGY

3-4 Cores: Formalin (all in one container) going to Pathology for:

- Diagnostic IHC
- Research IHC panel (see antibody panel below)
- DNA and RNA extraction for Lymphotrack test (to be given to DMP lab)
- Nanostring Immune Panel (to be given to DMP lab)
-

4 Cores: **RPMI** (all in one container) going to Pathology for:

- Diagnostic flow
- Research multiparameter flow cytometry (see antibody panel below)

2 Cores*: **Snap frozen** at HOTB and stored

PHELOBOTOMY

1 Purple Top Tube going to Pathology for clinical and research flow

2 Green Top Tubes going to HOTB for PBMC storage

1 Red Top Tube for HOTB for serum cytokines assay

*The snap frozen samples are optional and should only be taken if they can be safely obtained without any additional risk to the patient.

IHC panel

1. CD3
2. CD4
3. CD8
4. MHC-I
5. MHC-II
6. Beta2 microglobulin
7. PD1
8. PDL1
9. PDL2
10. CD68
11. FoxP3
12. Tbet
13. GATA3

Flow Cytometry Multiparameteric panel BD X50 machine

1. CD3
2. CD4
3. CD8
4. CD28
5. CD127
6. CD25
7. CD122
8. CD132
9. CD95
10. CD69
11. CD62L
12. CD45RO
13. LAG3
14. TIM3
15. PD1
16. CD56
17. CD16
18. CD10
19. CD19
20. CD20
21. CD27
22. CD38
23. CD138
24. IgM
25. IgG

Appendix 1
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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) and the Medical Monitor.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over $\geq$1 month to the equivalent of $\leq$ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for $>$ 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for $>$ 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for $>$ 12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

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

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

Table 1

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

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

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

LFT = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	Permanently discontinue atezolizumab and contact Medical Monitor. Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.
Diarrhea or colitis, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset. a Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If event 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.
Diarrhea or colitis, Grade 3	Withhold atezolizumab for up to 12 weeks after event onset. a Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone and taper over ≥ 1 month. If event resolves to Grade 1 or better, resume atezolizumab. b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. c

GI = gastrointestinal.

a Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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.

Event	Management
Diarrhea or colitis, Grade 1	Continue atezolizumab. Initiate symptomatic treatment. Endoscopy is recommended if symptoms persist for >7 days. Monitor closely.
Diarrhea or colitis, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset. [a] Initiate symptomatic treatment. Patient referral to GI specialist is recommended. For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	Withhold atezolizumab for up to 12 weeks after event onset. [a] Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

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

Event	Management
Diarrhea or colitis, Grade 4	Permanently discontinue atezolizumab and contact Medical Monitor.[c] Refer patient to GI specialist for evaluation and confirmation biopsy. Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

Event	Management
Asymptomatic hypothyroidism	Continue atezolizumab. Initiate treatment with thyroid replacement hormone. Monitor TSH weekly.
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.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** Continue atezolizumab. Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** Follow guidelines for symptomatic hyperthyroidism.
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 and contact Medical Monitor for life-threatening immune-related hyperthyroidism. [c]

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2 4	Withhold atezolizumab for up to 12 weeks after event onset. [a] Refer patient to endocrinologist. Perform appropriate imaging. Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	Continue atezolizumab. Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	Withhold atezolizumab. Initiate treatment with insulin. Monitor for glucose control. Resume atezolizumab when symptoms resolve and glucose levels are stable.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 4 Management Guidelines for Endocrine Events (cont.)

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

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

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

Table 5.

Table 5 Management Guidelines for Ocular Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Table 6 Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. Refer patient to cardiologist. Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. Consider treatment with corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related myocarditis, Grade 3-4	Permanently discontinue atezolizumab and contact Medical Monitor. [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 corticosteroids equivalent to 1 2 mg/kg/day IV methylprednisolone and convert to 1 2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

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

IRR = infusion-related reaction.

[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 rechallenged with atezolizumab only after approval has been documented by both the investigator (or assigned appropriate delegate) and the Medical Monitor.

Management Guidelines for Infusion-Related Reactions

PANCREATIC EVENTS

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

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

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

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	Continue atezolizumab. Investigate etiology.
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 and contact Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	Permanently discontinue atezolizumab and contact Medical Monitor. [c] Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	Permanently discontinue atezolizumab and contact Medical Monitor. [c] Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of corticosteroids equivalent to 1 2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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.

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

[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 both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

RENAL EVENTS

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes,

and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

Table 12

Event	Management
Renal event, Grade 1	Continue atezolizumab. Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	Withhold atezolizumab for up to 12 weeks after event onset. [a] Refer patient to renal specialist. Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. If event resolves to Grade 1 or better, resume atezolizumab. [b] If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	Permanently discontinue atezolizumab and contact Medical Monitor. Refer patient to renal specialist and consider renal biopsy. Initiate treatment with corticosteroids equivalent to 1 2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Management Guidelines for Renal Events

IMMUNE-RELATED MYOSITIS

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

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

Table 13

Table 13

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Management Guidelines for Immune-Related Myositis

Table 13 Management Guidelines for Immune-Related Myositis (cont.)

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

SYSTEMIC IMMUNE ACTIVATION

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 for atezolizumab.

Recommendations regarding early identification and management of systemic immune activation are provided below. In the event of suspected systemic immune activation, atezolizumab should be withheld and clinical specialists (e.g., rheumatology, clinical immunology, or solid organ or hematopoietic stem cell transplant specialists) and the Medical Monitor should be consulted for additional guidance.

Early disease recognition is critical, and systemic immune activation should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge
  - Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care
  - Supplemental oxygen and intubation may be required.
- Fever $>$ 38.5°C
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, or coagulopathy

For patients with suspected systemic immune activation, an initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Soluble interleukin 2 (IL-2) receptor (soluble CD25)
- Triglycerides
- AST, ALT, and direct bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of systemic immune activation exists.

If neurologic abnormalities are present, consider cerebrospinal fluid analysis and/or an MRI of the brain.

If cytopenias are present (Grade ≥ 2 in two or more lineages) or ferritin is ≥ 3000 ng/mL, the following evaluations should also be performed:

Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)

Adenovirus, cytomegalovirus, Epstein-Barr virus, herpes-simplex virus, and human herpesvirus 6, 7, and 8 evaluation (for reactivated or active disease)

Diagnostic criteria and recommended management for systemic immune activation are provided in

Table 14. The diagnostic criteria apply only when alternative etiologies have been excluded.

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
Fever ≥ 38.5°C on more than one occasion Ferritin ≥ 3000 ng/mL Cytopenias (Grade ≥ 2 in two or more lineages) Age-adjusted soluble interleukin-2 receptor elevated by ≥ 2 standard deviations Severe (Grade ≥ 3) or progressive dysfunction in two or more organs Decreased fibrinogen	Splenomegaly Hemophagocytosis in bone marrow, spleen, or lymph nodes Elevated γ-glutamyl transpeptidase (GGT) or liver function tests (AST, ALT, or direct bilirubin) Elevated triglycerides Elevated LDH Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥ 4 major criteria	Consistent with systemic immune activation	Permanently discontinue atezolizumab. Consider treatment with an immunosuppressive agent (i.e., cytokine inhibitors) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent, or dexamethasone ≥ 10 mg/m2 once daily if neurologic abnormalities are present). Contact the Medical Monitor for additional recommendations. Consider HLH-2004 protocol (Henter et al. 2007) if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable systemic immune activation	Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis. Clinical specialists and the Medical Monitor may be contacted for recommendations.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible systemic immune activation	Withhold atezolizumab. Consider treatment with IV corticosteroids. Clinical specialists and the Medical Monitor may be contacted for additional recommendations. Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs. If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).
Grades are based on National Cancer Institute Common Terminology Criteria for A Events.
These recommendations do not replace clinical judgment and are intended as suggested guidance.

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Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).
Grades are based on National Cancer Institute Common Terminology Criteria for A Events.
These recommendations do not replace clinical judgment and are intended as suggested guidance.

An adverse event of systemic immune activation should be reported on the Adverse Event eCRF if it meets the criteria for "consistent with systemic immune activation" or "probable systemic immune activation" as outlined in

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
Fever ≥ 38.5°C on more than one occasion Ferritin ≥ 3000 ng/mL Cytopenias (Grade ≥ 2 in two or more lineages) Age-adjusted soluble interleukin-2 receptor elevated by ≥ 2 standard deviations Severe (Grade ≥ 3) or progressive dysfunction in two or more organs Decreased fibrinogen	Splenomegaly Hemophagocytosis in bone marrow, spleen, or lymph nodes Elevated γ-glutamyl transpeptidase (GGT) or liver function tests (AST, ALT, or direct bilirubin) Elevated triglycerides Elevated LDH Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥ 4 major criteria	Consistent with systemic immune activation	Permanently discontinue atezolizumab. Consider treatment with an immunosuppressive agent (i.e., cytokine inhibitors) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent, or dexamethasone ≥ 10 mg/m2 once daily if neurologic abnormalities are present). Contact the Medical Monitor for additional recommendations. Consider HLH-2004 protocol (Henter et al. 2007) if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable systemic immune activation	Depending on clinical severity, follow guidelines for “Consistent with systemic immune activation” or “Possible systemic immune activation” diagnosis. Clinical specialists and the Medical Monitor may be contacted for recommendations.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible systemic immune activation	Withhold atezolizumab. Consider treatment with IV corticosteroids. Clinical specialists and the Medical Monitor may be contacted for additional recommendations. Follow guidelines for “Consistent with systemic immune activation” diagnosis if there is no clinical improvement or if clinical worsening occurs. If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).

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Grades are based on National Cancer Institute Common Terminology Criteria for A Events.
These recommendations do not replace clinical judgment and are intended as suggested guidance.

Table 14.

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
Fever ≥38.5°C on more than one occasion Ferritin ≥3000 ng/mL Cytopenias (Grade ≥2 in two or more lineages) Age-adjusted soluble interleukin-2 receptor elevated by ≥ 2 standard deviations Severe (Grade ≥3) or progressive dysfunction in two or more organs Decreased fibrinogen	Splenomegaly Hemophagocytosis in bone marrow, spleen, or lymph nodes Elevated γ-glutamyl transpeptidase (GGT) or liver function tests (AST, ALT, or direct bilirubin) Elevated triglycerides Elevated LDH Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥ 4 major criteria	Consistent with systemic immune activation	Permanently discontinue atezolizumab. Consider treatment with an immunosuppressive agent (i.e., cytokine inhibitors) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent, or dexamethasone ≥10 mg/m^2 once daily if neurologic abnormalities are present). Contact the Medical Monitor for additional recommendations. Consider HLH-2004 protocol (Henter et al. 2007) if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable systemic immune activation	Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis. Clinical specialists and the Medical Monitor may be contacted for recommendations.
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible systemic immune activation	Withhold atezolizumab. Consider treatment with IV corticosteroids. Clinical specialists and the Medical Monitor may be contacted for additional recommendations. Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs. If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).
Grades are based on National Cancer Institute Common Terminology Criteria for Adverse Events.
These recommendations do not replace clinical judgment and are intended as suggested guidance.

Table 14 Diagnostic Criteria and Recommended Management for Systemic Immune Activation