PROTOCOL

TITLE: **A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) ADMINISTERED INTRAVENOUSLY AS A SINGLE AGENT TO PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES**

PROTOCOL NUMBER: PCD4989g

VERSION NUMBER: A9

EUDRACT NUMBER: 2011-001422-23

IND NUMBER: 111271

TEST PRODUCT: Atezolizumab (RO5541267)

MEDICAL MONITOR: Redacted

SPONSOR: Genentech, Inc.

DATE FINAL: 13 May 2011

DATES AMENDED:
Version A1: 11 January 2012
Version A2: 16 March 2012 (UK Only)
Version A3: 18 May 2012
Version A4: 28 November 2012
Version A5: 16 August 2013
Version A6: 30 April 2014
Version A7: 27 June 2014
Version A8: 28 October 2015
Version A9: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
Redacted	Company Signatory	01-Dec-2016 19:52:44

PROTOCOL AMENDMENT, VERSION A9:
RATIONALE

Protocol PCD4989g has been amended to update the following:

- On the basis of updated clinical data regarding the atezolizumab half-life of 27 days, the following changes have been implemented:

  The period during which female patients must remain abstinent or use contraception and the length of follow-up of pregnancy reporting has been revised from 90 days to 5 months after the last dose of atezolizumab (Sections 4.1.1.1 and 5.3.1.9).

  The period during which patients must agree not to receive live, attenuated vaccine has been revised from 90 days to 5 months after the last dose of atezolizumab (Sections 4.1.2 and 4.4.1).

- To remove the whole blood collection for exploratory biomarker circulating tumor cell analysis as referenced in the study protocol
- On the basis of a review of clinical data, Epstein-Barr Virus testing is no longer required and has been removed from the protocol
- On the basis of a review of clinical data, TNBK collection is no longer required and has been removed from the protocol
- To clarify the monitoring schedule of thyroid-stimulating hormone TSH (Appendix 1)
- To clarify the bone scan requirement for prostate cancer patients (Section 4.5.1.4)
- To clarify the re-treatment and return to treatment process and the length of the follow up period after completion of 16 cycles for subjects enrolled before or under Amendment 5 and those currently in follow up (Section 3.1)

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION A9:
SUMMARY OF CHANGES

GLOBAL CHANGES

The words “fresh” or “freshly” were changed to “newly collected.”

The statement “on treatment” was changed to “during treatment.”

Additional minor changes have been made to improve clarity and consistency.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION PROTOCOL AMENDMENT ACCEPTANCE FORM

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SECTION 1.4.1: Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator’s Brochure for study descriptions). The single-agent safety and efficacy data available to date are from the following two studies:

- Study PCD4989g *(Study GO27831)*: a Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single-agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- ~~Study GO28753 (POPLAR): a randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single-agent versus docetaxel in PD-L1-unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.~~
- *POPLAR, BIRCH, and FIR are three ongoing, Phase II studies of patients with NSCLC. As of 1 December 2015, 938 patients with NSCLC from these three studies (POPLAR =142; BIRCH =659; FIR =137) had received atezolizumab as a single agent. Including the 89 safety-evaluable patients from the ongoing Phase Ia Study PCD4989g with a CCOD of 15 December 2015, 1027 patients with NSCLC in the 1L, 2L, and 3L +settings have been exposed to atezolizumab monotherapy.*

Refer to the Atezolizumab Investigator’s Brochure for details regarding safety and efficacy in these studies.

SECTION 1.4.2: 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. As of 15 *December 2015, 629* patients *have been treated with atezolizumab administered q3w in Study PCD4989g at doses ranging from 0.01 mg to 20 mg/kg across multiple tumor types.*

SECTION 1.4.3: Adverse Events

Of the ~~558~~*629* patients *who were evaluable for safety*, ~~520~~*619* ~~(93~~*8.24%)~~ patients *(98.4%)* experienced at least one adverse event, *regardless of attribution to atezolizumab.* The majority of these adverse events were Grade 1 or 2 in maximum severity on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Commonly reported adverse events (occurring in ≥10% of *patients who had been* treated ~~patients~~) included fatigue, nausea, decreased appetite, *diarrhea, constipation, dyspnea, pyrexia, cough, vomiting, anemia, back pain, headache, asthenia, arthralgia, pruritus, rash, abdominal pain, peripheral edema, urinary tract infection, insomnia, and dizziness.*

Approximately half of the 629 patients (50.2%) experienced an adverse event of Grade 3–4 in severity of which 86 (13.7%) were considered related. Of these, fatigue and asthenia (1.3% each), AST increased and dyspnea (1.1% each), and hyponatremia (0.8%) as the most frequently occurring (≥0.8% or ≥5 patients).~~Treatment-related adverse events (per investigator's assessment of causality) were reported in 67% of patients.~~

~~Refer to the Atezolizumab Investigator's Brochure for additional information.~~

SECTION 1.4.4: Immune-~~Mediated~~ *Related* 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~~*Potential immune-related events that have been reported include* dermatologic, hepatic, *gastrointestinal (GI),* endocrine, *neurologic,* and respiratory events as well as ~~events of hepatitis/elevated liver function tests and~~ influenza-like illness~~, which are considered potential adverse drug reactions associated with atezolizumab~~.

Refer to the Atezolizumab Investigator's Brochure for details regarding immune-related adverse events and identified risks (Adverse Drug Reactions) observed in patients treated with atezolizumab as well as recommended management guidelines for atezolizumab specific immune-related adverse events.

~~For further details, see the Atezolizumab Investigator's Brochure.~~

SECTION 1.4.5: Clinical Activity

~~Among 345 evaluable patients who were treated by 21 October 2013 (data cutoff date of 21 April 2014) with a median of 30.4 weeks of follow-up, 62 patients experienced objective responses per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) with an overall response rate (ORR) of 18% (95% CI: 14.1%, 22.3%). Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UBC, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The median DOR was 77.6 weeks (range: 6.4+ to 97.9+ weeks, where "+" denotes censored value). The majority of these responses have been durable, with 72.6% (45 of 62) of responses ongoing as of the clinical cutoff date.~~

Refer to the Atezolizumab Investigator's Brochure for updated details on clinical activity ~~in all patients treated to date, regardless of tumor type~~*from individual cohorts of study PCD4989g treated to date*.

SECTION 1.4.6: Clinical Pharmacokinetics and Immunogenicity

~~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 apparent clearance (CL) and the mean Vss had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.~~

A Phase I population PK analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range of 1–20 mg/kg with a linear two-compartment disposition model with first-order elimination. The population PK analysis indicated that central compartment volume of distribution was 3.28 L and the V_{ss} was 6.91 liters in the typical patient. Further, the CL of atezolizumab was 0.20 L/day and the time for drug in the body to be reduced by one-half was 27 days. Following q3w dosing, steady-state was obtained after 6–9 weeks (two to three cycles) of repeated dosing.

SECTION 3.1: DESCRIPTION OF THE STUDY

Based on long-term follow up data from the ongoing PCD4989g study, the treatment duration in Study PCD4989g has been modified. Prior to Amendment 6 of the protocol, patients were treated for 16 cycles (or 1 year; whichever came first) and then discontinued treatment. Patients who experienced disease progression after treatment had been stopped were allowed to be re-treated with atezolizumab within a 2-year off-treatment window.

Finally, patients who were enrolled prior to Amendment 6, completed 16 cycles of therapy, and entered the follow-up period (2-year window without treatment) before Amendment 6 was effective, remain eligible to return for treatment since these patients were enrolled when the re-treatment option was allowed per protocol. Those patients who have completed the 2-year follow-up window may still be able to

return-to-treatment. The acceptable length of time after the 2-year window is completed will be ascertained on a case by case basis, following agreement between the investigator and the Medical Monitor prior to initiating re-treatment.

Currently, the following 2 categories of patients can still exercise the re-treatment option:

- *Patients enrolled under Amendment 5 or earlier amendments who have completed the first 16 cycles (or 1 year, whichever came first) of therapy and who are still within the 2-year window (off-therapy) follow-up may return to exercise the re-treatment option.*

Patients enrolled under Amendment 5 or earlier amendments who have completed the first 16 cycles (or 1 year, whichever came first) of therapy and who are outside the 2-year follow-up window may return to exercise the re-treatment option following agreement between the investigator and Medical Monitor.

SECTION 3.1.2: Dose-Expansion Cohort

The expansion cohorts will include approximately:

20 patients with tumors that are amenable to serial biopsy *tissue collections* will also be enrolled at the selected dose and schedule. Serial tumor biopsies will be performed for those 20 patients but will be optional for all other patients (see Section 4.5.1). If a patient within the serial biopsy *tissue collection* cohort discontinues from the study before at least two interpretable tumor biopsy *tissue* samples are obtained (i.e., screening and ~~on~~*while patient is receiving* treatment), the patient will be replaced.

SECTION 3.1.3: Survival Follow-Up

Following treatment discontinuation, all patients will be followed for survival. At the time of implementation of ~~Protocol~~ Amendment 6, survival status will be assessed for all patients and dates of death reported for any patients who are deceased. For patients discontinued from the study before signing the updated informed consent under ~~Protocol~~ Amendment 6, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

SECTION 3.2.8: Rationale for Blood Sampling for Biomarkers

An exploratory objective is to evaluate changes in surrogate PD markers (~~T, B, and natural killer [TBNK] cell enumeration,~~ T-cell subpopulations, and other exploratory biomarkers) in blood samples that are relevant because of the target expression. Assessment of changes in these factors may provide evidence for biological activity of atezolizumab in humans.

Limited data suggest that certain circulating PD markers (e.g., chemokine ligand ITAC) peak within 8–21 days after atezolizumab infusion. In order to define the PD profile of the early circulating biomarkers, which may be associated with immune-mediated adverse events, Cycle 1, Days 8 and 15 blood samples will be collected from the first

50 patients enrolled in the dose expansion cohorts after the implementation of ~~Protocol~~ Amendment 7.

SECTION 3.2.10: Rationale for the Collection of Optional ~~Fresh~~ *Newly Collected* Tumor Specimens

The assessment of PD-L1/PD-1 pathway inhibition in tumor tissue would provide confirmation of the appropriate dose and exposure for atezolizumab for future studies. If both pre-treatment and ~~on-~~*during* treatment serial tissue biopsy samples (e.g., at the time of response or progression) can be obtained with minimal risk and discomfort to patients, patients will be requested, via separate consent forms for the optional biopsy, to provide biopsy samples for the study of PD changes related to the activity of atezolizumab (changes in infiltration of CD8+ T cells and other exploratory biomarkers). Additionally, a limited number of patients may be enrolled in a dose-expansion cohort in which patients will undergo pre-treatment and ~~on-~~*during* treatment serial biopsies.

SECTION 3.2.11: Rationale for the Collection of Tumor Specimens at the Time of Initial Radiological Progression

In order to characterize the kinetics and biological basis of the potential anti-tumor activity of atezolizumab, all patients will undergo a mandatory tumor biopsy *tissue* sample collection, if clinically feasible, at the first evidence of early radiographic disease progression (i.e., not preceded by meaningful tumor regression).

~~SECTION 3.2.12: Rationale for the Collection of Blood for Circulating Tumor Cells~~

~~Cancer patients with advanced disease have circulating tumor cells (CTCs) in their blood. CTCs, when isolated and enumerated, can be informative of patient's response to therapy and overall prognosis (Cristofanilli et al. 2004; de Bono et al. 2008). CTCs can also serve as a surrogate (non-tissue) source of tumor material that can be used for molecular analysis to understand a patient's current disease, particularly if there are changes in tumor genetics from collected archival tissue (Punnoose et al. 2010). Blood samples collected from patients for the analysis of CTCs will be used for the enumeration of CTCs and the evaluation of PD-L1 status with use of the CellSearch CTC assay (Attard et al. 2009) or a best available assay. Other potential predictive markers that are related to the PD-L1 pathway may also be analyzed if guided by either nonclinical or clinical data. This will not be performed in patients with hematologic malignancies.~~

SECTION 3.3.4: Exploratory Outcome Measures

The following exploratory PD endpoints will be assessed when appropriate:

- ~~Changes in TBNK numbers (TBNK assay) in blood~~
- Changes in various T-cell subpopulations in blood (e.g., effector/memory T cells, regulatory T cells, and other T-cell types)

- Identification and profiling of exploratory biomarkers in PBMCs (e.g., changes in expression of CD25 or human leukocyte antigen DR [HLA-DR], interferon [IFN]-γ production, and other markers)
- Changes in tumor-infiltrating, CD8+ T cells (and other exploratory markers) in ~~freshly~~*newly* obtained tumor tissue *samples* before and ~~on~~ *during* atezolizumab treatment
- Identification and profiling of exploratory biomarkers in plasma (i.e., interleukin [IL]-2, IFN-γ, and other markers)
- Changes in tumor-infiltrating T-cell activity (measured by expression of granzyme B and other markers) in ~~freshly~~*newly* obtained tumor tissue prior to and during atezolizumab treatment

SECTION 3.4.1: Risks Associated with Atezolizumab

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 guideline procedures for suspected immune-~~mediated~~ *related* adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

SECTION 3.4.3: Management of Specific Safety Concerns

Although most immune-~~mediated~~*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, mycophenolate, or tumor necrosis factor alpha (TNF–α) inhibitors.

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

See the Atezolizumab Investigator's Brochure for details on management of GI, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, ~~potential~~ pancreatic*, neurologic* or *potential* eye toxicity, and other immune-~~mediated~~ *related* adverse events.

SECTION 3.6: ADMINISTRATIVE STRUCTURE

Central laboratories will coordinate the collection of archival and ~~fresh~~ *newly collected* pre-treatment and during treatment tumor tissue (as applicable) and of blood samples for the assessment of PK, PD, and predictive biomarkers.

SECTION 4.1.1.1: General Inclusion Criteria

- Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, requested at any time prior to study entry.

  For patients with HCC, a core needle biopsy of the liver lesion is required during the screening period (archival tumor tissue could be submitted prior to the submission of ~~fresh~~ *newly collected* tumor tissue).

- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):

  If laboratory test values meet eligibility criteria during screening, but ~~fall out of window~~ *do not meet the eligibility criteria* on Cycle 1, Day 1, the patient may still be eligible for treatment with Medical Monitor approval following a discussion with the investigator.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least ~~90 days~~*5 months* after the last dose of atezolizumab

- INR and aPTT $\leq 1.5 \times$ ULN

  This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low–molecular weight heparin or warfarin) should be ~~on~~*receiving* a stable dose.

SECTION 4.1.1.2: Inclusion Criteria Unique to Patients Undergoing Serial Biopsy in the Serial Biopsy Dose-Expansion Cohort

- Baseline tumor tissue samples consisting of core needle biopsies for deep tumor tissue or organs or excisional or punch biopsies for cutaneous or subcutaneous lesions will be obtained. For cutaneous or subcutaneous lesions, tumors should be ≥ 5 mm in diameter amenable to serial biopsy by excisional or punch biopsies without unacceptable risk of a major procedural complication and at least two accessible lesions should be present (one for pre-treatment biopsy, one for ~~on~~-*biopsy sample collection during* treatment ~~biopsy~~).

SECTION 4.1.2.1: General Exclusion Criteria

- Known primary CNS malignancy or symptomatic CNS metastases (see Appendix 9 for disease-specific criteria for patients with GBM)

  Patients with asymptomatic untreated CNS disease may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:

No ongoing requirement for dexamethasone for CNS disease; patients ~~on~~*receiving* a stable dose of anticonvulsants are permitted

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

  Patients with a history of autoimmune hypothyroidism ~~on~~*receiving* a stable dose of thyroid replacement hormone may be eligible.

  Patients with controlled Type 1 diabetes mellitus ~~on~~*receiving* a stable insulin regimen may be eligible.

- History of HIV infection or active hepatitis B (chronic or acute) *defined as having a positive hepatitis B surface antigen (HBsAg) test at screening* or hepatitis C infection *defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening* (see Appendix 9 for disease-specific criteria for patients with HCC)

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test. Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study *or within 5 months following the last dose of atezolizumab*

  Influenza vaccination should be given during influenza season only (approximately October ~~to~~*through* Ma~~rch~~*y in the Northern Hemisphere and approximately April through September in the Southern Hemisphere*). Patients must *agree* not receive live, attenuated influenza vaccine (e.g., FluMist®) ~~within 4 weeks~~ *28 days* prior to Cycle 1, Day 1*, during treatment,* or ~~at any time during the study~~ *within 5 months following the last dose of atezolizumab*.

SECTION 4.3.1: Formulation

Atezolizumab ~~(MPDL3280A)~~ will be provided in the following configurations:

The two formulations for the atezolizumab drug product are not to be used interchangeably during the study. In general, patients enrolled before the implementation of ~~Protocol~~ Amendment 6 will receive Phase I formulation throughout their course of treatment. Patients enrolled after the implementation of ~~Protocol~~ Amendment 6 will use Phase III formulation throughout their course of treatment.

SECTION 4.3.2: Dosage, Administration, and Storage

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.3.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

SECTION 4.3.3: Dosage Modification

Any toxicity 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 immune-~~mediated~~*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.

For management of treatment-related adverse events and immune-*related* adverse events, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

SECTION 4.4.1: Concomitant Therapy

Concomitant therapy includes any ~~prescription~~ medication~~s~~ *(e.g., prescription drugs,* ~~or~~ over-the-counter ~~preparations~~ *drugs, vaccines, herbal or homeopathic remedies, nutritional supplements)* used by a patient ~~between the~~*from* 7 days preceding the screening evaluation and the treatment discontinuation visit. *All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.*

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.2*) may be used during the study at the discretion of the investigator.*

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 randomization, during treatment or within 5 months following the last of atezolizumab but may receive inactivated vaccine.

SECTION 4.4.2: Excluded Therapy

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

- *Denosumab (a RANKL inhibitor) is prohibited during the atezolizumab treatment because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead during atezolizumab treatment.*

~~It is strongly recommended that:~~

- ~~Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity~~
- ~~The use of a RANKL inhibitor (denosumab) be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab~~

SECTION 4.5: STUDY ASSESSMENTS

~~Flowcharts of scheduled study assessments are provided in~~ *See* Appendix 1–Appendix 4 *for the schedule of activities to be performed during the study.*

SECTION 4.5.1.1: Informed Consent Forms and Screening Log

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

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

SECTION 4.5.1.2: Medical History *and Demographic Data*

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

SECTION 4.5.1.5: Tumor and Response Evaluation Patients with Prostate Cancer

Bone scans are required to assess tumor progression in prostate patients by modified PCWG2 criteria. Therefore, if bone lesions are observed at baseline, then bone scans are to be done at same frequency as CT scans, at the time of the protocol-specified tumor assessment (i.e., every 6 or 12 weeks).

For patients who do not have bone lesions at baseline, bone scans will be initiated when the investigator feels that bone scans are clinically warranted. These should be done at the time of the protocol-specified tumor assessment. If bone lesions develop in the study, then bone scans should continue to be done at the same frequency as CT scans (i.e., every 6 or 12 weeks).

SECTION 4.5.1.6: Laboratory Assessments

Samples for hematology, serum chemistries, coagulation, urinalysis, and the *serum* pregnancy test will be analyzed at the study site's local laboratory. Central laboratories will coordinate the collection of archival tumor, ~~fresh~~ *newly collected* tumor, and leftover tumor tissue and blood samples for the assessment of atezolizumab pharmacokinetics and PD biomarkers, ATA assays, and auto-antibody testing.

Local laboratory assessments will include the following:

- ~~EBV serology (EBNA IgG)~~
- HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen)

  HBV DNA test is required for any patients who have positive serology for anti-HBc and patients with HCC who have positive serology for HBsAg. *Consider consultation with a virologist to monitor for HBV reactivation.*
- Biomarker assays

  … For the first approximately 50 patients enrolled after implementation of ~~Protocol~~ Amendment 7, blood will be obtained on Days 8 and 15 of Cycle 1. A detailed blood sampling schedule is provided in Appendix 3 and Appendix 4.
- ~~Biomarker analysis in CTCs (excluding hematologic malignancies)~~

  ~~Blood samples will be obtained for CTC evaluation from all eligible patients at screening, Cycle 1, Day 1 (before dosing), Cycle 3, Day 1 (before dosing), at the time of progression or response, and at the treatment discontinuation visit. Blood samples will be used for the enumeration of CTCs and the evaluation of PD-L1 expression with use of the CellSearch CTC assay. Other potential predictive markers that are related to the PD-L1 pathway may also be analyzed if guided by either nonclinical or clinical data.~~
- For patients in the dose-expansion cohort who are undergoing serial biopsies:

  Ideally, patients should have at least two accessible liver lesions amenable to core needle biopsies without unacceptable risk of a major procedural complication (one pre-treatment and at least one ~~on-~~*during* treatment biopsy will be performed; minimum diameter, 18 gauge). Two or three lesions should be present, and if possible, successive passes should be ≥ 1 cm apart. At least 3 cores should be collected from each lesion.

  ~~On-~~*During* Treatment Biopsy

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

SECTION 4.5.2: Assessments during Screening and after Confirmation of Eligibility

The following will be obtained from patients who are either in the dose-expansion cohort requiring serial biopsies or who have signed the Optional Research Informed Consent Form:

- Pre-treatment and ~~on-~~*during* treatment ~~fresh~~ *newly collected* tumor tissue

SECTION 4.5.3: Assessments during Treatment

~~On-~~*During* treatment ~~fresh~~ *newly collected* tumor biopsy samples will be obtained from patients who have signed the Optional Research Informed Consent Forms and for patients who are in the dose-expansion cohort requiring serial biopsies.

SECTION 4.5.5.1: Ongoing Tumor Assessments

In order to allow for more flexibility for patients who do not clinically require frequent scans, tumor assessments for patients that have discontinued treatment but remain in active follow up should be performed ***at least*** *every 6 months, but may be done more frequently as clinically indicated per discretion of the investigator.*

SECTION 4.6: PATIENT, *TREATMENT, STUDY, AND SITE* DISCONTINUATION

SECTION 4.6.1: *Patient and Study Treatment 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 or Sponsor determines may jeopardize the patient's safety if he or she continues in the study*
- *Investigator or Sponsor determines it is in the best interest of the patient*

~~Patients may withdraw from the study at any time.~~ Any patient who withdraws will be encouraged to return to the study center for a follow-up visit. Patients who discontinue treatment should return within 30 days of discontinuation (see Section 4.5.4). *Every effort should be made to obtain information on patients who withdraw from the study.* The primary reason for discontinuation must be recorded on the appropriate eCRF. *However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will be replaced.*

Patients must be withdrawn from the study if they experience any of the following:

- Intolerability to atezolizumab, including development of an immune-~~mediated~~*related* adverse event determined by the investigator and Medical Monitor to be unacceptable given the individual patient's potential response to therapy and severity of the event

SECTION 4.6.2: Study *and Site* Discontinuation

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor 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 ICH guideline for GCP*
- *No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)*

SECTION 4.7: POST-STUDY ACCESS

*Currently, the Sponsor (*Genentech*, a member of the Roche Group)* does not ~~intend~~ *have any plans* to provide atezolizumab or other study interventions to patients ~~after the conclusion of~~ *who have completed* the study or any earlier withdrawal. *The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:*

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

SECTION 5.1: SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording ~~protocol-defined~~ adverse events~~, and~~ *including* serious adverse events *and adverse events of special interest*, *performing* ~~measurement of~~ protocol-specified ~~hematology, clinical chemistry, and urinalysis variables~~ *laboratory assessments*~~;~~, measur~~ement of~~*ing* protocol-specified vital signs; and *conducting* other protocol-specified tests that are deemed critical to the safety evaluation of the study ~~drug~~.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

SECTION 5.1.2: Serious Adverse Events

A serious adverse event is any adverse event that ~~is~~*meets* any of the following *criteria*:

- *Is* ~~F~~*f*atal (i.e., the adverse event actually causes or leads to death)
- *Is* ~~L~~*l*ife threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization *(see Section 5.3.1.8)*
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- *Is* ~~A~~*a* congenital anomaly/birth defect in a neonate/infant born to a mother exposed to ~~the investigational product~~*study drug*
- ~~Considered~~*Is* a significant medical event ~~by~~*in* the investigator*'s judgement* (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

~~All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.~~

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (*e.g., rated* as ~~in~~ mild, moderate, or severe ~~pain~~*, or according to*

NCI CTCAE); the event itself may be of relatively minor medical significance (such as severe headache *without any further findings*). ~~"Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.~~

Severity and seriousness ~~should~~ *need to* be independently assessed ~~when recording~~ *for each* adverse event~~s and serious adverse events~~ *recorded* on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

SECTION 5.2: METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events and serious adverse events (as defined in Section 5.1) are recorded on the *Adverse Event* eCRF and reported to the Sponsor in accordance with protocol instructions.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality.

SECTION 5.2.1: Adverse Event Reporting Period

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

SECTION 5.2.3: Assessment of Severity and Causality of Adverse Events

~~Note: The investigator's assessment of causality for individual adverse event reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual adverse event reports, the Sponsor will promptly evaluate all reported serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.~~

SECTION 5.3.1.9: Pregnancy

Abortion, ~~whether therapeutic or spontaneous,~~ should always be classified as serious (because the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor.

SECTION 7.3.1: Optional Research Informed Consent

If obtaining pre-treatment and ~~on-~~*during* treatment biopsy samples and remaining samples of tumor tissue for optional research described in Section 3.2.10 and Section 4.5.1 is approved by the IRB/EC, the consent form entitled "Sample Research Informed Consent Form" will be provided by Genentech to each study site.

APPENDIX 1: Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 2: Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 3: Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 4: Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Except the First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 7: Prostate Response Evaluation Criteria

Please refer to the Prostate guidance in the Appendix II of the CRF Completion Guidelines for additional information on how to assess progression of bone lesions and evaluate tumor response according to modified Prostate Cancer Working Group 2 (PCWG2) criteria.

- Soft tissue lesions

  Soft tissue lesions should be assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) *and immune-related Response (irRC)* criteria (see Appendix 5 *and* Appendix 6).

APPENDIX 8: Revised Assessment in Neuro-Oncology Criteria for Patients with Glioblastoma

See Table 1 for an overview of types of lesions.

APPENDIX 9: Tumor-Type Specific Inclusion and Exclusion Criteria

GLIOBLASTOMA MULTIFORME

Exclusion criteria:

- Ongoing requirement for dexamethasone

  Patients ~~on~~*receiving* a stable dose of anticonvulsants are permitted.

HEPATOCELLULAR CARCINOMA

Inclusion criteria:

- Willing to undergo ~~fresh~~*newly collected* liver biopsy

U.S. SAMPLE INFORMED CONSENT FORM

The U.S. sample Informed Consent Form has been updated to reflect changes in the protocol.

E.U. SAMPLE INFORMED CONSENT FORM

The E.U. sample Informed Consent Form has been updated to reflect changes in the protocol.

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PROTOCOL AMENDMENT FINALIZATION SIGNATURE PAGE

TITLE:	**A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) ADMINISTERED INTRAVENOUSLY AS A SINGLE AGENT TO PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES**
PROTOCOL NUMBER:	PCD4989g
EUDRACT NUMBER:	2011-001422-23
STUDY DRUG:	Atezolizumab
IND NUMBER:	111271
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	Redacted
SPONSOR:	Genentech, Inc.
DATE FINAL:	13 May 2011
DATES AMENDED:	Version A1: 11 January 2012 Version A2: 16 March 2012 (UK Only) Version A3: 18 May 2012 Version A4: 28 November 2012 Version A5: 16 August 2013 Version A6: 30 April 2014 Version A7: 27 June 2014 Version A8: 28 October 2015 Version A9: See the electronic date stamp on the title page.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) ADMINISTERED INTRAVENOUSLY AS A SINGLE AGENT TO PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES**
PROTOCOL NUMBER:	PCD4989g
VERSION NUMBER:	A9
EUDRACT NUMBER:	2011-001422-23
IND NUMBER:	111271
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	Redacted
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the original signed copy in your study files and provide a copy to Genentech at the address provided below.

Redacted

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) ADMINISTERED INTRAVENOUSLY AS A SINGLE AGENT TO PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES**
PROTOCOL NUMBER:	PCD4989g
EUDRACT NUMBER:	2011-001422-23
IND NUMBER:	111271
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	I
INDICATION:	Locally advanced or metastatic solid tumors or hematologic malignancies
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety, pharmacokinetics, and activity of atezolizumab in patients with locally advanced or metastatic solid tumors or hematologic malignancies. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objectives

- To evaluate the safety and tolerability of atezolizumab administered by intravenous (IV) infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To determine the maximum tolerated dose (MTD) and to evaluate the dose-limiting toxicities (DLTs) of atezolizumab when administered as a single-agent to patients by IV infusion q3w
- To identify a recommended Phase II dose of atezolizumab

Secondary Objectives

Pharmacokinetic Objectives

- To evaluate the pharmacokinetics of atezolizumab when administered as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To characterize the immunogenic potential of atezolizumab by measuring anti-atezolizumab antibodies

Activity Objective

- To make a preliminary assessment of the anti-tumor activity of atezolizumab administered as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies

Exploratory Objectives

- To make a preliminary assessment of biomarkers that might act as pharmacodynamic (PD) indicators of anti-tumor activity of atezolizumab administered as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To make a preliminary assessment of biomarkers that might act as predictors of anti-tumor activity of atezolizumab administered as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To evaluate overall survival (OS)

Study Design

Description of Study

This Phase I, multicenter, first-in-human, open-label, dose-escalation study will evaluate the safety, tolerability, and pharmacokinetics of atezolizumab administered as a single-agent by IV infusion q3w to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

Approximately eight dose levels ranging from 0.01 to 20 mg/kg (the proposed doses are 0.01, 0.03, and 0.1 mg/kg as single-patient cohorts and 0.3, 1, 3, 10, and 20 mg/kg as 3 + 3 cohorts) will be evaluated to determine the MTD or the maximum administered dose (MAD) of atezolizumab in the dose-escalation stage of the study. Depending on new nonclinical efficacy, clinical safety, and clinical pharmacokinetic (PK) data, additional intermediate dose levels and/or different schedules (with dosing no more frequently than once a week) may be evaluated during the dose-escalation stage after consultation with the study investigators.

Prior to determination of the MTD or MAD, additional patients may be enrolled and treated in expansion cohorts at doses of ≤ 10 mg/kg to better characterize the safety, tolerability, PK variability, and preliminary efficacy of single-agent atezolizumab. Up to approximately 10 patients with renal cell carcinoma (RCC), 10 patients with melanoma, and 10 patients with non–small cell lung cancer (NSCLC) may be enrolled in each expansion cohort, after the 10-mg/kg dose level has been determined to be safe in a minimum of 3 patients.

After determination of the MTD or MAD, additional patients will be enrolled and treated in expansion cohorts at doses and schedules selected to result in a total drug exposure less than or equal to exposures achieved at the MTD or MAD. In order to further characterize the safety of atezolizumab and to assess biomarkers of tumor activity in different cancer types, the expansion cohorts will include approximately:

- 40 patients with RCC
- 40 patients with NSCLC
- 20 patients with melanoma
- 495 patients with solid tumors or hematologic malignancies may be enrolled. After discussion with the study investigators, prospective enrollment of patients may be based on potential predictive tumor characteristics (e.g., programmed death–ligand 1 [PD-L1] + status; in the United States, this applies only in Investigational Device Information [IDI] indications after IDI submission to the Center for Devices and Radiological Health [CDRH]).
- 20 patients with tumors that are amenable to serial biopsy tissue collection will also be enrolled at the selected dose and schedule. Serial tumor biopsies will be performed for those 20 patients but will be optional for all other patients.

This study will be conducted at approximately 25 sites in the United States and outside the United States. The sample size for this study will be determined by dose-escalation rules and the number and size of expansion cohorts. Approximately 656–689 patients will be enrolled in this study.

All patients will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. All adverse events will be recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, only ongoing serious adverse events determined by the investigator to be related to treatment will be recorded. Additionally, patients with unresolved adverse events or

abnormal laboratory values deemed related to study treatment may be contacted by telephone for follow up of these events. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0].

To characterize the PK properties of atezolizumab, blood samples will be taken at various timepoints before and after study treatment administration. Blood sampling for PD analyses will be synchronized with select blood draws for the PK studies. Blood samples will be taken approximately every 30 (±14) days for up to 120 days after study treatment has been discontinued because high levels of atezolizumab may mask detection of anti–therapeutic antibodies [ATAs].

For patients with solid malignancies (except for prostate cancer), study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both the Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1] and the immune-related response criteria (irRC)
- Do not meet the criteria to continue dosing after Cycle 1
- Are not compliant with the study protocol

For patients with prostate cancer, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by Prostate Cancer Response Criteria and confirmed by repeat assessment ≥3 weeks after the initial response evaluation
- Do not meet the criteria to continue dosing after Cycle 1
- Are not compliant with the study protocol

For patients with glioblastoma multiforme (GBM), study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both Revised Assessment in Neuro-Oncology (RANO) Response Criteria and irRC)
- Do not meet the criteria to continue dosing after Cycle 1
- Are not compliant with the study protocol

For patients with malignant lymphoma, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both the Revised International Working Group (IWG) Response Criteria and the irRC
- Do not meet the criteria to continue dosing after Cycle 1
- Are not compliant with the study protocol

For patients with multiple myeloma, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by the International Myeloma Working Group (IMWG) Uniform Response Criteria and confirmed by repeat assessment ≥4 weeks after the initial response evaluation
- Do not meet the criteria to continue dosing after Cycle 1
- Are not compliant with the study protocol

Patients who experience a DLT will not be allowed to continue to receive study treatment and will be followed for safety.

Patients will be offered atezolizumab treatment beyond Cycle 1 as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation.

Patients who demonstrate radiographic disease progression per RECIST v1.1 for solid tumors; per RANO Response Criteria for GBM that has not been confirmed by irRC; per 2007 Revised

IWG Response Criteria for malignant lymphoma that has not been confirmed by irRC; per Prostate Cancer Response Criteria that has not been confirmed by repeat assessment; or per IMWG Uniform Response Criteria for multiple myeloma that has not been confirmed by repeat assessment may be considered for continued study treatment if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory test values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Patients who demonstrate confirmed radiographic disease progression according to: both RECIST v1.1 and irRC (solid tumors); both the 2007 Revised IWG Response Criteria and irRC (malignant lymphoma); both the IMWG Uniform Response Criteria and repeat assessment ≥ 4 weeks after the initial response evaluation (multiple myeloma); or both RANO Response Criteria and irRC (GBM); or both the Prostate Cancer Response Criteria and repeat assessment ≥ 3 weeks after the initial response evaluation (prostate cancer) may be considered for continued study treatment at the discretion of the investigator following discussion with the Medical Monitor, provided they continue to meet all the criteria above and have evidence of clinical benefit.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until death, disease progression, or initiation of further systemic cancer therapy or until the study closes, whichever occurs first.

Based on long-term follow up data from the ongoing PCD4989g study, the treatment duration in Study PCD4989g has been modified. Prior to Amendment 6 of the protocol, patients were treated for 16 cycles (or 1 year; whichever came first) and then discontinued treatment. Patients who experienced disease progression after treatment had been stopped were allowed to be re-treated with atezolizumab within a 2-year off-treatment window.

Finally, patients who were enrolled prior to Amendment 6, completed 16 cycles of therapy, and entered the follow-up period (2-year window without treatment) before Amendment 6 was effective, remain eligible to return for treatment since these patients were enrolled when the re-treatment option was allowed per protocol. Those patients who have completed the 2-year follow-up window may still be able to return-to-treatment. The acceptable length of time after the 2-year window is completed will be ascertained on a case by case basis, following agreement between the investigator and the Medical Monitor prior to initiating re-treatment.

Currently, the following 2 categories of patients can still exercise the re-treatment option:

- Patients enrolled under Amendment 5 or earlier amendments who have completed the first 16 cycles (or 1 year, whichever came first) of therapy and who are still within the 2-year window (off-therapy) follow-up may return to exercise the re-treatment option.
- Patients enrolled under Amendment 5 or earlier amendments who have completed the first 16 cycles (or 1 year, whichever came first) of therapy and who are outside the 2-year follow-up window may return to exercise the re-treatment option following agreement between the investigator and Medical Monitor.

Following treatment discontinuation and follow-up periods, all patients will be followed for survival until withdrawal of consent, loss of follow-up, death, or until study termination by the Sponsor, whichever occurs first.

Number of Patients

The planned enrollment for this study is approximately 656–689 patients, depending on the number and size of the cohorts. The study will enroll approximately 21–54 patients in the dose-escalation stage and approximately up to 635 patients in the dose-expansion stage.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years

  Adolescent patients who are 16–17 years old (body weight $\geq$ 40 kg) with one of the tumor types specified in this protocol would be considered for enrollment after discussion with and approval by the Medical Monitor.
- Histologically or cytologically documented, incurable or metastatic solid tumor or hematologic malignancy that is advanced (non-resectable) or recurrent and progressing since the last anti-tumor therapy and for which no recognized standard curative therapy exists.

  For all sites, patients who have completed pre-screening tumor characterization and who have signed the pre-screening consent form may be considered for enrollment in the solid tumor or hematologic malignancy dose-expansion cohort on the basis of PD-L1 status. In the United States, this will apply only after submission of the IDI to the CDRH.
- Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, requested at any time prior to study entry. Only tissue from core needle, punch, or excisional biopsy sample collection will be accepted. Fine-needle aspiration, brushing, and lavage samples are not acceptable. For all biopsy types, submitted blocks should have sufficient tissue to generate at least 15 sections, and tissue for which the pathology report specifies that the overall tumor content is low (e.g., "sparse" or "scant") is not acceptable. Tissue from separate timepoints (such as time of initial diagnosis and time of metastatic diagnosis) or from the multiple metastatic tumors may also be collected for a given patient, on the basis of availability.

  For patients in the dose-expansion cohorts, archival tumor tissue must be confirmed to be available prior to study entry.

  If archival tissue is either insufficient or unavailable, the patient may still be eligible upon discussion with the Medical Monitor if the patient can provide at least five unstained, serial slides or is willing to consent to and undergo a pre-treatment core or excisional biopsy sample collection of the tumor. Fine-needle aspiration, brushing, and lavage samples are not acceptable.

  For patients with hepatocellular carcinoma (HCC), a core needle biopsy of the liver lesion is required during the screening period (archival tumor tissue could be submitted prior to the submission of newly collected tumor tissue).
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):

  ANC $\geq$ 1500 cells/μL

  WBC counts $>$ 2500/μL

  Lymphocyte count $\geq$ 500/μL

  Platelet count $\geq$ 100,000/μL; for patients with hematologic malignancies, platelet count $\geq$ 75,000/μL

  Hemoglobin $\geq$ 9.0 g/dL

  Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

  Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

AST and ALT $\leq 3.0 \times$ ULN with the following exception:

Patients with liver involvement: AST and/or ALT $\leq 5 \times$ ULN

Alkaline phosphatase $\leq 2.5 \times$ ULN with the following exception:

Patients with documented liver involvement or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

If laboratory test values meet eligibility criteria during screening, but do not meet the eligibility criteria on Cycle 1, Day 1, the patient may still be eligible for treatment with Medical Monitor approval following a discussion with the investigator.

- Measurable disease per RECIST v1.1 for patients with solid malignancies

  Disease-specific criteria will be used for patients with prostate cancer, GBM, malignant lymphoma, or multiple myeloma:

  Prostate cancer: measurable disease from progression defined by at least one of the following:

  Prostate-specific antigen (PSA) progression according to Prostate Cancer Working Group 2 (PCWG2) criteria: PSA level of at least 2 ng/mL which has subsequently risen on at least two successive occasions at least 2 weeks apart. If the second risen value is lower than the first risen value, then an additional test for rising PSA will be required to document progression. The value of the additional test must be higher than the first risen value.

  Radiographic progression in soft tissue or bone lesions

  GBM: bi-dimensionally measurable disease with a minimum measurement of 1 cm in one diameter on magnetic resonance imaging (MRI) performed within 14 days prior to first treatment (Day 0)

  Baseline MRIs for patients who underwent salvage surgery after first relapse must be obtained ≥ 4 weeks after the procedure. If receiving corticosteroids, patients must be on a stable or decreasing dose of corticosteroids for ≥ 5 days prior to baseline MRI.

  Malignant lymphoma: at least one bi-dimensionally measurable lesion measuring > 1.5 cm in its largest dimension by computed tomography (CT) scan

  Multiple myeloma: measurable disease defined by at least one of the following: monoclonal protein in the plasma of ≥ 1.0 g/dL; monoclonal protein in the urine of ≥ 0.2 g/24-hour urine collection; or serum Ig free light chain (FLC) ≥ 100 mg/L (10 mg/dL) and an abnormal serum immunoglobulin kappa to lambda FLC ratio

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 5 months after the last dose of atezolizumab

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established proper use of 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 study 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.

- ECOG performance status of 0 or 1

  Patients with ECOG performance status of 2, secondary to the underlying disease, may be enrolled after consultation with the Medical Monitor.

  Karnofsky Performance Status ≥ 70 for patients with GBM

- INR and aPTT $\leq 1.5 \times$ ULN

  This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low–molecular weight heparin or warfarin) should be receiving a stable dose.

Inclusion Criteria Unique to Patients Undergoing Serial Biopsy in the Serial Biopsy Dose-Expansion Cohort

Baseline tumor tissue samples consisting of core needle biopsies for deep tumor tissue or organs or excisional or punch biopsies for cutaneous or subcutaneous lesions will be obtained. For cutaneous or subcutaneous lesions, tumors should be ≥ 5 mm in diameter amenable to serial biopsy by excisional or punch biopsies without unacceptable risk of a major procedural complication and at least two accessible lesions should be present (one for pre-treatment biopsy, one for biopsy sample collection during treatment). For core needle biopsy specimens, at least three cores should be submitted for evaluation. If more than one biopsy is planned to be taken from one lesion, the lesion must be large enough to permit successive biopsies ≥ 1 cm apart. An additional biopsy sample may be collected per investigator discretion, preferably at the time of radiographic progression or response.

Exclusion Criteria

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

- Any approved anti-cancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:

  Hormonal therapy with gonadotropin-releasing hormone (GnRH) agonists or antagonists for prostate cancer

  Hormone-replacement therapy or oral contraceptives

  Herbal therapy > 1 week prior to Cycle 1, Day 1 (herbal therapy intended as anti-cancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)

  Palliative radiotherapy for bone metastases > 2 weeks prior to Cycle 1, Day 1

- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia
- Bisphosphonate therapy for symptomatic hypercalcemia

  Use of bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) is allowed.

- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease
- Patients with acute leukemia, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma
- Known primary CNS malignancy or symptomatic CNS metastases

  Patients with asymptomatic untreated CNS disease may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:

  Evaluable or measurable disease outside the CNS

  No metastases to brain stem, midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)

No history of intracranial hemorrhage or spinal cord hemorrhage

No ongoing requirement for dexamethasone for CNS disease; patients receiving a stable dose of anticonvulsants are permitted

No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1

Patients with asymptomatic treated CNS metastases may be enrolled after consultation with the Medical Monitor, provided all the criteria listed above are met as well as the following:

Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

No stereotactic radiation or whole-brain radiation within 28 days prior to Cycle 1, Day 1

Screening CNS radiographic study $\geq$ 4 weeks from completion of radiotherapy and $\geq$ 2 weeks from discontinuation of corticosteroids

- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to pharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Inability to comply with study and follow-up procedures
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune hypothyroidism receiving a stable dose of thyroid replacement hormone may be eligible.

  Patients with controlled Type 1 diabetes mellitus receiving a stable insulin regimen may be eligible.

  Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

  Patients with psoriasis must have a baseline ophthalmologic examination to rule out ocular manifestations

  Rash must cover less than 10% of 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 PUVA [psoralen plus ultraviolet A radiation], 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 CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory test result 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) defined as having a positive hepatitis B surface antigen (HBsAg) test at screening or hepatitis C infection defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening

Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

The HCV RNA test will be performed only for patients who have a positive HCV antibody test. Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Active tuberculosis
- Patients in dose-escalation cohorts: absence of Epstein-Barr virus (EBV) antibodies (negative EBV serology, negative Epstein-Barr nuclear antigen [EBNA] IgG)
- Severe infections within 4 weeks prior to Cycle 1, Day 1 including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients who are receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- 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 or anticipation that such a live attenuated vaccine will be required during the study or within 5 months following the last dose of atezolizumab

  Influenza vaccination should be given during influenza season only (approximately October through May in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Patients must agree not receive live, attenuated influenza vaccine (e.g., FluMist®) 28 days prior to Cycle 1, Day 1, during treatment, or within 5 months following the last dose of atezolizumab.
- Malignancies other than disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., CLL Rai Stage 0, prostate cancer with Gleason score ≤ 6, and PSA ≤ 10 mg/mL, etc.)

<u>Exclusion Criteria Related to Medications</u>

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

  Patients who have received prior treatment with anti–CTLA-4 may be enrolled, provided the following requirements 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 (CTCAE Grade 3 and 4)
- Treatment with systemic immunostimulatory agents (including but not limited to IFN-α, IL-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF agents) within 2 weeks prior to Cycle 1, Day 1

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

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

End of Study

The last patient will be enrolled October 2016.

Length of Study

The duration of the study is approximately 18 months.

Investigational Medicinal Products

Atezolizumab will be provided in the following configurations:

- The atezolizumab drug product produced using the Phase I manufacturing process is provided in a single-use, 2-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 1.2 mL (150 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 1.2 mL volume. The atezolizumab drug product is formulated as 125 mg/mL atezolizumab in 20 mM histidine acetate, 240 mM sucrose, 0.02% polysorbate 20, pH 5.5 (Phase I formulation).
- The atezolizumab drug product produced using the Phase III manufacturing process 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 (Phase III formulation).

The two formulations for the atezolizumab drug product are not to be used interchangeably during the study. In general, patients enrolled before the implementation of Amendment 6 will receive Phase I formulation throughout their course of treatment. Patients enrolled after the implementation of Amendment 6 will use Phase III formulation throughout their course of treatment. The guidelines regarding the assignment of study treatment formulations may be further modified on the basis of availability of the Phase I or Phase III formulation and will be communicated to the sites.

The dose levels of atezolizumab in the Phase I formulation tested in this study include 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 20 mg/kg administered by IV infusion q3w (21 [$\pm$2] days). Additional intermediate dose levels and/or different schedules of atezolizumab may be tested on the basis of new nonclinical efficacy, clinical safety, and clinical PK data at the time and after discussions with the investigators. The atezolizumab dose will be based on the patient's weight (in kilograms) measured $\leq$14 days before baseline (Cycle 1, Day 1). It is not necessary to correct dosing on the basis of ideal body weight. For dose levels of 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg, doses will be prepared by diluting atezolizumab with diluent (formulation buffer) into an empty sterile vial. For dose levels $\geq$14 mg/kg, no dilution is required.

The dose level of atezolizumab in the Phase III formulation proposed 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 q3w (21 [$\pm$2] days).

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 ($\pm$15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 ($\pm$10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ($\pm$10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes

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

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥2 at the discretion of the treating physician after consultation with the Medical Monitor. The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, 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 infusion-related event (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 infusion-related event.
- For severe or life-threatening infusion-related events (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 infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

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. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days preceding the screening evaluation and the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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 TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥2 at the discretion of the treating physician after consultation with the Medical Monitor. 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. Planned use of other medications should be discussed with the Medical Monitor.

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

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 randomization, during treatment or within 5 months following the last of atezolizumab but may receive inactivated vaccine.

Patients who use hormonal therapy with GnRH agonists or antagonists for prostate cancer, oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low–molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use. Males and females of reproductive potential should use highly effective means of contraception. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Statistical Methods

Primary Analysis

The final analysis will be based on patient data collected through study discontinuation. The analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of atezolizumab. In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. All summaries will be presented by the assigned dose level or tumor type, when appropriate.

Determination of Sample Size

Design considerations were not made with regard to explicit power and type I error considerations but were made to obtain preliminary safety, PK, and PD information in this patient population. The planned enrollment for this study is approximately 656–689 patients, depending on the number and size of the cohorts. The study will enroll approximately 21–54 patients in the dose-escalation stage and approximately up to 635 patients in the dose-expansion stage. Within each indication (e.g., RCC, melanoma, NSCLC) of the expansion cohort, the following rule will apply: if no responders (CR or PR) are observed from the first 14 patients who are considered to be more likely to respond on the basis of the presence of biomarkers potentially predictive of anti-tumor activity, enrollment will be suspended for that indication. With the assumption of a true response rate of 20% or higher, there is at most a 4.4% chance of not observing any response in 14 patients.

With an observed response rate of 30%, a sample size of 40 patients within a given indication (i.e., RCC, NSCLC) will result in a 90% CI of 19.96%–42.87%. The corresponding 90% CI with 20 patients will be 16.39%–48.38%.

Any patient who does not complete the DLT assessment window for any reason other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level.

To better characterize the safety of the single-agent MTD identified in the dose-escalation stage, additional expansion cohorts of approximately 40 patients (in RCC and NSCLC) will be enrolled. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in a given cohort of 6 patients is 47%, 26%, and 5.8%, respectively. The corresponding probabilities of observing at least one such adverse event in an expanded cohort of 40 patients will increase to 98.5%, 87.1%, and 33.1%, respectively.

Safety Analyses

Safety will be assessed through summaries of DLTs, adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to atezolizumab. All patients who receive any amount of atezolizumab will be included in the safety analyses.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse event data will be listed by study site, dose cohort, treatment arm, patient number, and study day. Events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. In addition, serious adverse events, including deaths, will be listed separately and summarized.

Adverse events leading to treatment discontinuation will be listed. Adverse events leading to the declaration of DLTs will be listed. Patients who withdraw from the study prior to completing the DLT assessment window (Day 21) for reasons other than a DLT will be considered unevaluable for DLT and MTD assessments.

Relevant laboratory and vital signs data will be displayed by time, with NCI CTCAE Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by grade with use of NCI CTCAE v4.0.

Incidence of ATA response and the potential correlation with PK, PD, and safety parameters may be assessed.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AFP	alpha-fetoprotein
anti-HBc	antibody to hepatitis B core antigen
ATA	anti–therapeutic antibody
AUC	area under the concentration–time curve
BSA	body surface area
CA	cancer antigen
CDRH	Center for Devices and Radiological Health
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CL	total clearance of drug
CR	complete responses
CRC	colorectal cancer
CT	computed tomography
CTC	circulating tumor cell
C_{trough}	target trough concentration
DLT	dose-limiting toxicity
DOR	duration of response
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
EC_{50}	50% effective concentrations
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Reporting Form
EDC	electronic data capture
FACS	fluorescence-activated cell sorting
FDA	U.S. Food and Drug Administration
FDG	^{18}fluorodeoxyglucose
FLC	free light chain
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GI	Gastrointestinal
GnRH	gonadotropin-releasing hormone
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus

Abbreviation	Definition
HDV	hepatitis D virus
HIPAA	Health Insurance Portability and Accountability Act
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IDI	Investigational Device Information
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
irRC	immune-related response criteria
IWG	International Working Group
IV	Intravenous
IxRS	interactive voice/Web response system
LCMV	clone 13 variant of lymphocytic choriomeningitis virus
MAD	maximum administered dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NSCLC	non–small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCWG2	Prostate Cancer Working Group 2
PD	pharmacodynamics
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
q3w	every 3 weeks
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
RANO	Revised Assessment in Neuro-Oncology
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
SD	stable disease
SDV	source data verification
SPEP/IFE	serum protein electrophoresis/immunofixation electrophoresis
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UBC	urothelial bladder carcinoma
ULN	upper limit of normal
UPEP/IFE	urine protein electrophoresis/immunofixation electrophoresis
V_{ss}	volume at steady state
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON THE MOLECULE

Atezolizumab (MPDL3280A) is a humanized IgG1 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 programmed death–ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death–1 (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.

1.2 SUMMARY OF NONCLINICAL STUDIES

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.

Refer to the Atezolizumab Investigator's Brochure for details on the nonclinical studies. A brief summary is provided below.

1.2.1 Nonclinical Pharmacology

Several in vitro studies have been conducted to characterize the binding of atezolizumab to its target PD-L1, as well as its ability to block the binding of this glycoprotein to its known receptors PD-1 and B7-1.

In more detail, equilibrium binding analysis demonstrated that atezolizumab binds to human and murine PD-L1 expressed on transfected 293 cells with sub-nanomolar affinities ($K_d = 0.433$ nM and 0.134 nM, respectively). These high affinities were confirmed in flow cytometry experiments with use of human T cells and murine PD-L1–expressing 293 cells, showing 50% effective concentrations (EC_{50}) of 0.395 ± 0.030 nM and 0.519 ± 0.025 nM for human and mouse, respectively.

A comparable affinity to PD-L1 was determined in cynomolgus monkey T cells ($EC_{50} = 0.704 \pm 0.084$ nM).

Furthermore, atezolizumab blocked binding of human recombinant PD-L1 to its target receptor PD-1 (50% inhibitory concentration [IC_{50}] $= 82.8 \pm 40.3$ pM) and to B7-1 ($IC_{50} = 48.4 \pm 25.9$ pM), as measured by an enzyme-linked immunosorbent assay (ELISA).

Finally, atezolizumab-dependent cytokine release from human peripheral blood mononuclear cells (PBMCs) was not detected following in vitro culture with immobilized or soluble atezolizumab at concentrations approximately 750-fold above the expected maximum observed concentration at the proposed starting dose, suggesting that the risk for exaggerated cytokine release associated with atezolizumab administration is low.

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

1.2.2 Nonclinical Pharmacokinetics

The pharmacokinetics of atezolizumab was characterized following a single IV dose of 0.5, 5, and 20 mg/kg in cynomolgus monkeys (Study 08-0598). The PK properties of atezolizumab were typical for IgG1 antibodies in cynomolgus monkeys. The mean plasma clearance (CL) was 3.70 mL/day/kg, the mean volume at steady state (V_{ss}) was similar to that of the plasma volume (59.8 mL/kg), and the mean beta-phase half-life was 11.5 days.

The toxicokinetics of atezolizumab was characterized in the repeat-dose toxicology study in cynomolgus monkeys following multiple IV doses with a range of 5–50 mg/kg given weekly for a total of nine doses (Study 08-1148). Linear dose-dependent systemic exposures were observed up to Day 7 in all dosed groups.

Human PK parameters were projected using the species invariant-time method (Dedrick 1973), incorporating results from the single-dose PK study in cynomolgus monkeys (Study 08-0598). The estimated mean CL value in humans was 1.98 mL/day/kg (range: 1.92–2.09 mL/day/kg). The estimated mean elimination half-life in humans was 21.5 days (range: 20.3–23.1 days). These parameters were used in calculating safety factors to support the starting dose in humans.

The proposed starting dose of atezolizumab in humans is 0.01 mg/kg administered intravenously. This dose is adequately supported by the 8-week, nonclinical toxicology study in cynomolgus monkeys (Study 08-1148). With use of the no observed adverse effect level (NOAEL) of 5 mg/kg and a human CL value of 1.98 mL/day/kg, the exposure (area under the concentration–time curve [AUC])–based safety factor is 268-fold. The single-dose, body weight–normalized, dose-based safety factor at the proposed Phase I starting dose of 0.01 mg/kg is 500-fold, and the safety factor based on the body surface

area (BSA)–normalized dose is approximately 160-fold. These safety factors are considered adequate to support the proposed Phase I starting dose of 0.01 mg/kg.

The pharmacokinetics and toxicokinetics of atezolizumab were characterized in cynomolgus monkeys. Overall, the nonclinical pharmacokinetics observed for atezolizumab support the proposed Phase I study, including providing adequate safety factors for the Phase I doses.

1.2.3 Nonclinical Toxicology

The toxicology program was designed to support IV administration of atezolizumab to patients up to every week for at least 2 months. The program included an 8-week, repeat-dose study in cynomolgus monkeys, a 15-day exploratory study in mice, an in vitro hemolytic potential evaluation, and a tissue cross-reactivity analysis of human and cynomolgus monkey tissues.

Atezolizumab was well tolerated in cynomolgus monkeys following IV doses of up to 50 mg/kg for 8 weeks (total of nine doses). Minimal-to-mild arteritis and/or periarteritis was observed in 1 of 12 and 3 of 12 cynomolgus monkeys following administration of 15 and 50 mg/kg atezolizumab, respectively. These findings were not present on Day 141, indicating apparent resolution during the recovery period. Spontaneous, sporadic arteritis and/or periarteritis has been observed in cynomolgus monkeys, suggesting that the monkeys may be predisposed to this form of autoimmune disorder (Chamanza et al. 2006).

Atezolizumab did not cause hemolysis of human or cynomolgus monkey erythrocytes at in vitro concentrations of up to 125 mg/mL (the highest testable concentration).

In human tissues, biotin-atezolizumab–specific staining was detected in the placenta, lymph node, tonsil, and thymus. In cynomolgus monkey tissues, biotin-atezolizumab–specific staining was detected only in the lymph node. This staining is consistent with the reported expression of PD-L1 on lymphoid and non-lymphoid tissues (Dong et al. 1999; Keir et al. 2007).

Taken together, the results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and support entry into this Phase I study in patients with locally advanced or metastatic solid tumors or hematologic malignancies.

1.3 SCIENTIFIC RATIONALE

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010). Therefore, immunomodulation represents a promising new strategy for cancer therapy resulting in improved anti-tumor activity.

PD-L1 is one of two ligands (PD-L1 and PD-L2) that binds PD-1, an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

PD-L1 expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, glioblastoma multiforme, malignant lymphoma, multiple myeloma, and colon carcinoma), and elevated PD-L1 expression is often associated with a worse prognosis in patients with several cancers including renal cell carcinoma (RCC), melanoma, colorectal cancer (CRC), lung cancer, ovarian cancer, and others. Furthermore, in mouse tumor models, interruption of the interaction between PD-1 and PD-L1 resulted in anti-tumor effects (Iwai et al. 2002; Strome et al. 2003): single-agent activity of PD-L1 blockade in the syngeneic CRC model MC-38, expressing the foreign antigen ovalbumin, resulted in complete responses (CRs) in all animals tested in fewer than 2 weeks of treatment (unpublished Genentech data). Finally, reports from three Phase I clinical studies testing cancer therapies targeting the PD-L1/PD-1 pathway have demonstrated activity in late-stage, standard-of-care–refractory patients with cancer. In a Phase I dose-escalation study of 207 patients treated with BMS-936559, an IgG4 anti–PD-L1 monoclonal antibody, Brahmer et al. (2012) observed a response rate of approximately 17% in patients with melanoma, 12% in patients with RCC, 10% in patients with non–small cell lung cancer (NSCLC), and 6% in patients with ovarian cancer. A Phase I dose-escalation study of 296 patients treated with BMS-936558, an IgG4 anti–PD-1 monoclonal antibody, reported a response rate of approximately 28% in patients with melanoma, 27% in patients with RCC, and 18% in patients with NSCLC (Topalian et al. 2012). In a Phase I study in which 17 patients were treated with CT-011, a humanized antibody interacting with PD-1, clinical benefit was observed in 33% of patients, with one CR (non-Hodgkin's lymphoma) and one major response (acute myelogenous leukemia) (Berger et al. 2008).

Atezolizumab targets PD-L1, thus inhibiting its interaction with the PD-1 receptor. In multiple mouse tumor models, comparable efficacy has been observed with the blocking of either the PD-1 receptor or the PD-L1 ligand. Atezolizumab was designed with an amino acid substitution that may reduce the incidence and severity of toxicities and potentially provide a greater therapeutic index.

Collectively, these data provide a compelling rationale to test whether inhibition of the PD-L1/PD-1 pathway with a humanized anti–PD-L1 IgG1 antibody with diminished effector function will result in an enhanced clinical benefit in patients with cancer.

1.4 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

1.4.1 Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the Atezolizumab Investigator's Brochure for study descriptions). The single-agent safety and efficacy data available to date are from the following two studies:

- Study PCD4989g *(Study GO27831)*: a Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single-agent by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- *POPLAR, BIRCH, and FIR are three ongoing, Phase II studies of patients with NSCLC. As of 1 December 2015, 938 patients with NSCLC from these three studies (POPLAR =142; BIRCH =659; FIR =137) had received atezolizumab as a single agent. Including the 89 safety-evaluable patients from the ongoing Phase Ia Study PCD4989g with a CCOD of 15 December 2015, 1027 patients with NSCLC in the 1L, 2L, and* 3L +settings *have been exposed to atezolizumab monotherapy.*

Refer to the Atezolizumab Investigator's Brochure for details regarding safety and efficacy in these studies.

1.4.2 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. As of 15 *December 2015, 629* patients *have been treated with atezolizumab administered q3w in Study PCD4989g at doses ranging from 0.01 mg to 20 mg/kg across multiple tumor types.*

Currently, no maximum tolerated dose, no dose-limiting toxicities 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 carcinoma (UBC), melanoma, and renal cell carcinoma. Safety data for NSCLC are also derived from Studies GO28625 (FIR) and GO28753 (POPLAR).

Refer to the Atezolizumab Investigator's Brochure for additional information.

1.4.3 Adverse Events

Of the *629* patients *who were evaluable for safety*, *619* patients *(98.4%)* experienced at least one adverse event, *regardless of attribution to atezolizumab.* The majority of these adverse events were Grade 1 or 2 in maximum severity on the basis of National

Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Commonly reported adverse events (occurring in ≥10% of *patients who had been* treated) included fatigue, nausea, decreased appetite, *diarrhea, constipation, dyspnea, pyrexia, cough, vomiting, anemia, back pain, headache, asthenia, arthralgia, pruritus, rash, abdominal pain, peripheral edema, urinary tract infection, insomnia, and dizziness.*

Approximately half of the 629 patients (50.2%) experienced an adverse event of Grade 3–4 in severity of which 86 (13.7%) were considered related. Of these, fatigue and asthenia (1.3% each), AST increased and dyspnea (1.1% each), and hyponatremia (0.8%) as the most frequently occurring (≥0.8% or ≥5 patients).

1.4.4 Immune-*Related* 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. *Potential immune-related events that have been reported include* dermatologic, hepatic, *gastrointestinal (GI),* endocrine, *neurologic,* and respiratory events as well as influenza-like illness.

Refer to the Atezolizumab Investigator's Brochure for details regarding immune-related adverse events and identified risks (Adverse Drug Reactions) observed in patients treated with atezolizumab as well as recommended management guidelines for atezolizumab specific immune-related adverse events.

1.4.5 Clinical Activity

Refer to the Atezolizumab Investigator's Brochure for updated details on clinical activity *from individual cohorts of study PCD4989g treated to date.*

Preliminary results from Study PCD4989g suggest that PD-L1 expression in tumor-infiltrating immune cells is likely to be associated with response to atezolizumab. PD-L1 positivity is currently defined as discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥5% of the tumor, which is defined as an immunohistochemistry (IHC) score of 2 or higher (i.e., IHC 2 or IHC 3). The prototype diagnostic IHC assay used in Study PCD4989g was analytically validated at this threshold. In the overall cohort of efficacy-evaluable patients with a variety of tumor types in Study PCD4989g, patients with IHC 2 or IHC 3 had a higher ORR at 24.8% compared with 14.8% in patients with IHC 0 or IHC 1.

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

1.4.6 Clinical Pharmacokinetics and Immunogenicity

A Phase I population PK analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range of 1–20 mg/kg with a linear two-compartment disposition model with first-order elimination. The population PK analysis indicated

that central compartment volume of distribution was 3.28 L and the V_{ss} was 6.91 liters in the typical patient. Further, the CL of atezolizumab was 0.20 L/day and the time for drug in the body to be reduced by one-half was 27 days. Following q3w dosing, steady-state was obtained after 6–9 weeks (two to three cycles) of repeated dosing.

The development of anti-therapeutic antibodies (ATAs) 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 to 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 adverse events or infusion reactions has been observed.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To evaluate the safety and tolerability of atezolizumab administered by IV infusion q3w to patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To determine the maximum tolerated dose (MTD) and to evaluate the dose-limiting toxicities (DLTs) of atezolizumab when administered as a single-agent to patients by IV infusion q3w
- To identify a recommended Phase II dose of atezolizumab

2.2 SECONDARY OBJECTIVES

2.2.1 Pharmacokinetic Objectives

- To evaluate the pharmacokinetics of atezolizumab when administered as a single-agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To characterize the immunogenic potential of atezolizumab by measuring anti-atezolizumab antibodies

2.2.2 Activity Objective

- To make a preliminary assessment of the anti-tumor activity of atezolizumab administered as a single-agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies

2.3 EXPLORATORY OBJECTIVES

- To make a preliminary assessment of biomarkers that might act as pharmacodynamic (PD) indicators of anti-tumor activity of atezolizumab administered as a single-agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies

- To make a preliminary assessment of biomarkers that might act as predictors of anti-tumor activity of atezolizumab administered as a single-agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To evaluate OS

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This Phase I, multicenter, first-in-human, open-label, dose-escalation study will evaluate the safety, tolerability, and pharmacokinetics of atezolizumab administered as a single-agent by IV infusion q3w to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

Approximately eight dose levels ranging from 0.01 to 20 mg/kg (the proposed doses are 0.01, 0.03, and 0.1 mg/kg as single-patient cohorts and 0.3, 1, 3, 10, and 20 mg/kg as 3+3 cohorts) will be evaluated to determine the MTD or the maximum administered dose (MAD) of atezolizumab in the dose-escalation stage of the study. Depending on new nonclinical efficacy, clinical safety, and clinical PK data, additional intermediate dose levels and/or different schedules (with dosing no more frequently than once a week) may be evaluated during the dose-escalation stage after consultation with the study investigators.

Prior to determination of the MTD or MAD, additional patients may be enrolled and treated in expansion cohorts at doses of ≤10 mg/kg to better characterize the safety, tolerability, PK variability, and preliminary efficacy of single-agent atezolizumab. Up to approximately 10 patients with RCC, 10 patients with melanoma, and 10 patients with NSCLC may be enrolled in each expansion cohort, after the 10-mg/kg dose level has been determined to be safe in a minimum of 3 patients.

After determination of the MTD or MAD, additional patients will be enrolled and treated in expansion cohorts at doses and schedules selected to result in a total drug exposure less than or equal to exposures achieved at the MTD or MAD. In order to further characterize the safety of atezolizumab and to assess biomarkers of tumor activity in different cancer types, the expansion cohorts will include approximately:

- 40 patients with RCC
- 40 patients with NSCLC
- 20 patients with melanoma
- 495 patients with solid tumors or hematologic malignancies may be enrolled. After discussion with the study investigators, prospective enrollment of patients may be based on potential predictive tumor characteristics (e.g., PD-L1+status; in the United States, this applies only in Investigational Device Information [IDI] indications after IDI submission to the Center for Devices and Radiological Health [CDRH]). See Section 3.1.2 for more details.

- 20 patients with tumors that are amenable to serial biopsy tissue collection will also be enrolled at the selected dose and schedule. Serial tumor biopsies will be performed for those 20 patients but will be optional for all other patients.

This study will be conducted at approximately 25 sites in the United States and outside the United States. The sample size for this study will be determined by the dose-escalation rules described in Section 3.1.1 and the number and size of expansion cohorts. Approximately 656–689 patients will be enrolled in this study.

All patients will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. All adverse events will be recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, only ongoing serious adverse events determined by the investigator to be related to treatment will be recorded. Additionally, patients with unresolved adverse events or abnormal laboratory values deemed related to study treatment may be contacted by telephone for follow up of these events. Adverse events will be graded according to the NCI CTCAE v4.0.

To characterize the PK properties of atezolizumab, blood samples will be taken at various timepoints before and after study treatment administration. Blood sampling for PD analyses will be synchronized with select blood draws for the PK studies (see Appendix 3 and Appendix 4). Blood samples will be taken approximately every 30 (±14) days for up to 120 days after study treatment has been discontinued because high levels of atezolizumab may mask detection of ATAs.

For patients with solid malignancies (except for prostate cancer), study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both the RECIST v1.1 (see Appendix 5) and the immune-related response criteria (irRC) (see Appendix 6)
- Do not meet the criteria to continue dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

For patients with prostate cancer, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by Prostate Cancer Response Criteria and confirmed by repeat assessment ≥3 weeks after the initial response evaluation (see Appendix 7)
- Do not meet the criteria to continue dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

For patients with glioblastoma multiforme (GBM), study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both Revised Assessment in Neuro-Oncology (RANO) Response Criteria (see Appendix 7) and irRC (see Appendix 6)
- Do not meet the criteria to continue dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

For patients with malignant lymphoma, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both the Revised International Working Group (IWG) Response Criteria (Cheson et al. 2007; see Appendix 12) and the irRC (see Appendix 6)
- Do not meet the criteria to continue dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

For patients with multiple myeloma, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by the International Myeloma Working Group (IMWG) Uniform Response Criteria and confirmed by repeat assessment $\geq$4 weeks after the initial response evaluation (Durie et al. 2006; see Appendix 13)
- Do not meet the criteria to continue dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

Patients who experience a DLT will not be allowed to continue to receive study treatment and will be followed for safety (see Section 3.1.1).

Patients will be offered atezolizumab treatment beyond Cycle 1 as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.6.

Patients who demonstrate radiographic disease progression per RECIST v1.1 for solid tumors; per RANO Response Criteria for GBM that has not been confirmed by irRC; per 2007 Revised IWG Response Criteria for malignant lymphoma that has not been confirmed by irRC; per Prostate Cancer Response Criteria that has not been confirmed by repeat assessment; or per IMWG Uniform Response Criteria for multiple myeloma that has not been confirmed by repeat assessment may be considered for continued study treatment if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory test values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease

- No decline in Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Patients who demonstrate confirmed radiographic disease progression according to: both RECIST v1.1 and irRC (solid tumors); both the 2007 Revised IWG Response Criteria and irRC (malignant lymphoma); both the IMWG Uniform Response Criteria and repeat assessment ≥4 weeks after the initial response evaluation (multiple myeloma); or both RANO Response Criteria and irRC (GBM); or both the Prostate Cancer Response Criteria and repeat assessment ≥3 weeks after the initial response evaluation (prostate cancer) may be considered for continued study treatment at the discretion of the investigator following discussion with the Medical Monitor, provided they continue to meet all the criteria above and have evidence of clinical benefit.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until death, disease progression, or initiation of further systemic cancer therapy or until the study closes, whichever occurs first.

Based on long-term follow up data from the ongoing PCD4989g study, the treatment duration in Study PCD4989g has been modified. Prior to Amendment 6 of the protocol, patients were treated for 16 cycles (or 1 year; whichever came first) and then discontinued treatment. Patients who experienced disease progression after treatment had been stopped were allowed to be re-treated with atezolizumab within a 2-year off-treatment window.

Finally, patients who were enrolled prior to Amendment 6, completed 16 cycles of therapy, and entered the follow-up period (2-year window without treatment) before Amendment 6 was effective, remain eligible to return for treatment since these patients were enrolled when the re-treatment option was allowed per protocol. Those patients who have completed the 2-year follow-up window may still be able to return-to-treatment. The acceptable length of time after the 2-year window is completed will be ascertained on a case by case basis, following agreement between the investigator and the Medical Monitor prior to initiating re-treatment.

Currently, the following 2 categories of patients can still exercise the re-treatment option:

- *Patients enrolled under Amendment 5 or earlier amendments who have completed the first 16 cycles (or 1 year, whichever came first) of therapy and who are still*

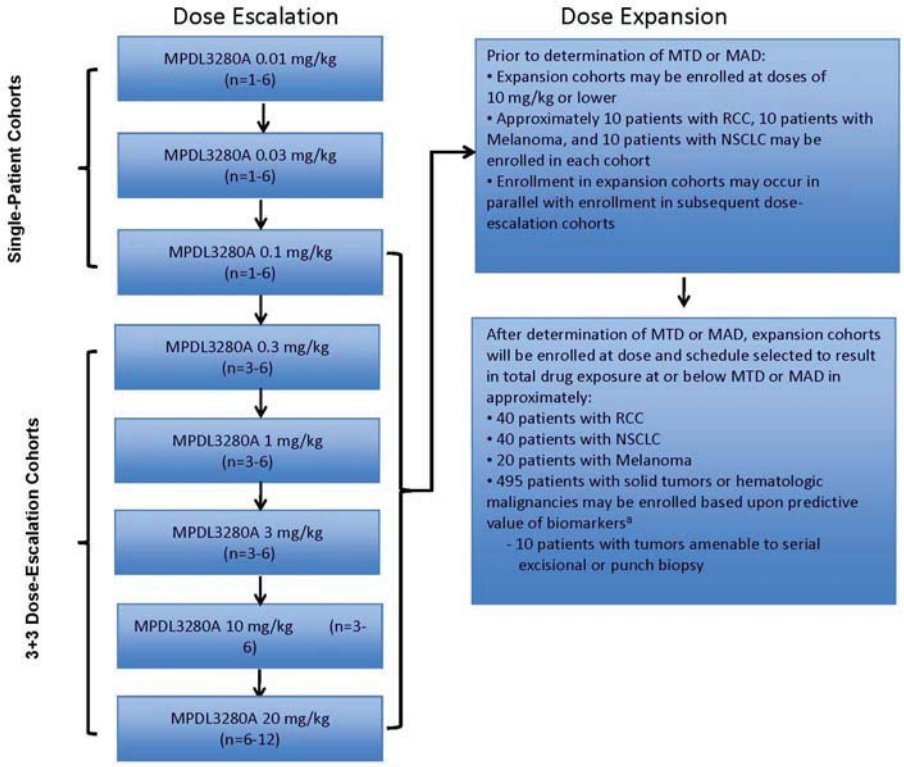
within the 2-year window (off-therapy) follow-up may return to exercise the re-treatment option.

- *Patients enrolled under Amendment 5 or earlier amendments who have completed the first 16 cycles (or 1 year, whichever came first) of therapy and who are outside the 2-year follow-up window may return to exercise the re-treatment option following agreement between the investigator and Medical Monitor.*

Following treatment discontinuation and follow-up periods, all patients will be followed for survival (see Section 3.1.3) until withdrawal of consent, loss of follow-up, death, or until study termination by the Sponsor, whichever occurs first.

The study design is depicted in Figure 1. Study procedures and assessments are further detailed in Section 4.5 and in Appendix 1–Appendix 4.

Figure 1 Study Design: Proposed Cohorts



IDI = investigational device information; MAD = maximum administered dose; MPDL3290A = atezolizumab; MTD = maximum tolerated dose; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; RCC = renal cell carcinoma.

[a] Prospective enrollment based on potential predictive tumor characteristics (e.g., PD-L1+ status; in the United States, only in IDI indications once IDI submitted to the Center for Devices and Radiological Health) may be implemented. See Section 3.1.2 for more details}

3.1.1 Dose-Escalation Stage

3.1.1.1 Starting Dose, Dose Escalation, and Dose-Limiting Toxicity Assessment Window

The starting dose of atezolizumab during the dose-escalation stage will be 0.01 mg/kg administered to patients by IV infusion q3w. In the absence of DLTs that prevent escalation to the next dose level, this study will evaluate a proposed total of eight dose levels: 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 20 mg/kg. Depending on new nonclinical efficacy, clinical safety, and clinical PK data, additional intermediate dose levels and/or different schedules may be evaluated.

Single-patient dose-escalation will be employed for the 0.01-, 0.03-, and 0.1-mg/kg cohorts, and a traditional 3+3 dose-escalation scheme will be used for the 0.3-, 1-, 3-, 10-, and 20-mg/kg cohorts. A minimum of 1 patient will be enrolled in each single-patient cohort and a minimum of 3 patients will be enrolled at each 3+3 dose level. If the first patient in a single-patient cohort or the first 3 patients enrolled in a 3+3 dose-escalation cohort complete dosing through the DLT assessment window without experiencing DLTs, patients may be enrolled at the next higher dose level.

The DLT assessment window will be 21 days following the first dose of atezolizumab (Days 1–21 of Cycle 1). Any patient who does not complete the DLT assessment window for any reason other than a DLT will be considered nonevaluable for dose-escalation decisions and the MTD assessment and will be replaced by an additional patient at that same dose level.

3.1.1.2 Rules of Dose Escalation and Changes in Dose Scheduling following Dose-Limiting Toxicity

Dose escalation will occur in accordance with the following rules:

- For dose cohorts receiving atezolizumab 0.01, 0.03, or 0.1 mg/kg: a minimum of 1 patient will be enrolled into each of these single-patient cohorts. In the absence of a DLT, dose escalation may proceed. If a DLT occurs in a cohort, that cohort will be expanded to a minimum of 6 patients (dosing in the expanded single-patient cohort[s] may be staggered by ≥24 hours depending on the nature of the DLT).
- For dose cohorts receiving atezolizumab ≥0.3 mg/kg: each of these 3+3 cohorts will initially enroll 3 patients. Dosing of the first 3 patients enrolled in the 0.3 mg/kg cohort only will be staggered by ≥24 hours. In the absence of a DLT, dose escalation may proceed. If a DLT occurs in a cohort, that cohort will be expanded to a minimum of 6 patients.
- If fewer than one-third of evaluable patients in a given cohort experiences a DLT (i.e., DLT in fewer than 1 of 3 or 2 of 6 patients), escalation may proceed to the next higher dose level.
- If a DLT is observed in 2 or more of 6 patients, the MTD will have been exceeded and dose escalation will be stopped. A minimum of 3 additional patients (if a 3+3 cohort) or a minimum of 5 additional patients (if a single-patient cohort) will

be evaluated for DLTs at the preceding dose level (if 6 patients had not already been dosed at that level).

- If the MTD is exceeded at a dose level, the previous highest dose level at which fewer than one-third of at least 6 patients experiences a DLT will be declared the MTD.
- If fewer than 2 of 6 evaluable patients at the highest dose level experiences a DLT, this dose level will be declared the MAD.

If the dose level at which the MTD is exceeded is $\geq$50% greater than the previous dose level, an intermediate dose level may be evaluated for toxicity in the same manner as described above.

3.1.1.3 Definition of Dose-Limiting Toxicity

A DLT is defined as one of the following toxicities occurring during the DLT assessment window considered to be possibly, probably, or definitely related to atezolizumab as described in Table 2:

- Grade $\geq$4 neutropenia (ANC $<$500/μL) lasting $\geq$7 days
- Grade $\geq$3 febrile neutropenia
- Grade $\geq$4 thrombocytopenia lasting $>$48 hours
- Any Grade $\geq$3 nonhematologic or nonhepatic major organ adverse event with the following exceptions:

  Grade 3 nausea, vomiting, or diarrhea that resolves to Grade $\leq$1 with or without treatment prior to the next infusion
- Any Grade $\geq$3 hepatic toxicity with the following exceptions:

  For patients with Grade 2 AST, ALT, and/or alkaline phosphatase abnormality at baseline, an increase in the baseline abnormality to $>10\times$ the upper limit of normal (ULN) will be considered a DLT.

3.1.1.4 Dose Modifications of Atezolizumab

If a patient does not receive the full assigned dose of atezolizumab during the DLT assessment window (Days 1–21 of Cycle 1) for reasons other than a DLT, the patient will be replaced.

Patients who experience a DLT will not be allowed to continue receiving study treatment and will be followed for safety.

Intrapatient dose escalation up to the MAD will be allowed for patients in dose levels below the MAD who have stable disease (SD) or clinical benefit, as assessed by investigator, after completing four cycles of atezolizumab treatment, provided that the patients have not experienced a drug-related major toxicity and the Medical Monitor has approved the dose escalation. The MAD is defined as the maximum dose level at which 6 patients have cleared the DLT window.

Atezolizumab should be withheld for new clinically significant infections. If atezolizumab is withheld because of adverse events for >84 days beyond the date the next dose should have been given, the patient will then be discontinued from atezolizumab and will be followed for safety.

3.1.1.5 Rules to Continue Dosing beyond Cycle 1

To continue dosing beyond Cycle 1, the following criteria must be met:

- Patients must not have experienced a DLT as described in Section 3.1.1.
- Patients must not have experienced unacceptable toxicities as deemed by the treating investigator.
- Patients must not have experienced disease progression, as defined by both RECIST v1.1 and irRC in patients with solid malignancies as assessed by both 2007 Revised IWG Response Criteria and irRC in patients with malignant lymphoma, or as assessed by both the IMWG Uniform Response Criteria and repeat assessment ≥4 weeks after the initial response evaluation in patients with multiple myeloma. If evidence of apparent pseudoprogression is present in patients with clinical benefit, patients may continue to receive study treatment at the discretion of the investigator and following discussion with the Medical Monitor. Patients with a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for three or fewer lesions may still be eligible to continue study treatment. Such cases must be discussed with and approved by the Medical Monitor.

3.1.2 Dose-Expansion Cohort

Prior to determination of the MTD or MAD, additional patients may be enrolled and treated in expansion cohorts at doses of ≤10 mg/kg to better characterize safety, tolerability, PK variability, and preliminary efficacy of single-agent atezolizumab. Up to approximately 10 patients with RCC, 10 patients with melanoma, and 10 patients with NSCLC will be enrolled in each expansion cohort after the 10-mg/kg dose level has been determined to be safe in a minimum of 3 patients. Enrollment in an expansion cohort may begin after all patients initially enrolled at that dose level have cleared the DLT assessment window and that dose has been determined to be safe. Enrollment in expansion cohorts may occur in parallel with enrollment in subsequent dose-escalation cohorts.

Additional patients will be enrolled and treated in expansion cohorts at doses and schedules selected to result in total drug exposure less than or equal to exposures achieved at the MTD or MAD. Determination of the dose and schedule to be expanded will be made by the Sponsor in consultation with the study investigators and will take into account the observed toxicities, tolerability, and pharmacokinetics of atezolizumab. The expansion cohorts will include approximately:

- 40 patients with RCC
- 40 patients with NSCLC

- 20 patients with melanoma
- 495 patients with solid tumors or hematologic malignancies may be enrolled on the basis of the potential predictive value of biomarkers (e.g., PD-L1+ status) (in the United States, this will apply only to IDI indications after submission of the IDI to the CDRH). This group of cohorts may comprise patients with NSCLC, RCC, head and neck cancer, gastric cancer, breast cancer, CRC, malignant lymphoma, multiple myeloma, prostate cancer, GBM, hepatocellular carcinoma (HCC), endometrial cancer, pancreatic cancer, and bladder cancer. An additional "basket cohort" will comprise patients with tumor types (e.g., ovarian, esophageal, sarcoma, Merkel cell, small cell lung cancer, cervical cancer, etc.) that will not have their own designated cohort. A maximum of approximately 20 patients with a particular histology (approximately 15 patients with hematologic malignancies) will be enrolled in this cohort unless anti-tumor activity and/or clinical benefit per investigator is detected in multiple patients (i.e., $\geq$2 of 10 patients) in a particular histology, in which case the maximum of 20 patients with a particular histology may be exceeded as decided by the Sponsor in consultation with study investigators.
- 20 patients with tumors that are amenable to serial biopsy *tissue collections* will also be enrolled at the selected dose and schedule. Serial tumor biopsies will be performed for those 20 patients but will be optional for all other patients (see Section 4.5.1). If a patient within the serial biopsy *tissue collection* cohort discontinues from the study before at least two interpretable tumor biopsy *tissue* samples are obtained (i.e., screening and *while patient is receiving* treatment), the patient will be replaced.

Safety and PK assessments, as well as the rules to continue dosing in the dose-expansion stage, will be identical to those in the dose-escalation stage.

If the frequency of Grade 3 or 4 toxicities or other unacceptable toxicities suggests that the MTD has been exceeded at a dose level and enrollment is still ongoing, any remaining accrual to the dose-expansion cohort(s) at or above that dose level will be halted. Consideration will then be given to enrolling patients in a dose-expansion cohort at a lower dose level.

3.1.3 Survival Follow-Up

Following treatment discontinuation, all patients will be followed for survival. At the time of implementation of Amendment 6, survival status will be assessed for all patients and dates of death reported for any patients who are deceased. For patients discontinued from the study before signing the updated informed consent under Amendment 6, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

After the initial survival assessment of all study patients, survival follow-up will occur every 3 months via clinic visits, telephone call, and/or review of patient medical records until patient death, loss to follow-up, withdrawal of consent, or until study termination by the Sponsor.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Patient Group Selection

The patient population selected for the dose-expansion stage of the study (patients with histologically or cytologically documented metastatic or incurable solid tumor or hematologic malignancy that is advanced [non-resectable] or recurrent and progressing since the last anti-tumor therapy and for which no recognized standard curative therapy exists) will primarily encompass patients whose tumors have progressed following approved therapies. In addition, given the preliminary safety and efficacy data from the solid tumor patients in the dose-escalation stage of this study and RECIST v1.1 responses reported with this and other PD-L1/PD-1 inhibitors, the patient population also includes patients with metastatic or incurable solid tumors or hematological malignancies for whom all therapies with known clinical benefit may not have been exhausted but for whom the risks of standard therapies may outweigh potential benefits. All patients need to sign the main informed consent as an acknowledgment of having been provided with alternative treatment options if available by their treating physicians before enrolling into the dose-expansion stage of this study.

The dose-expansion stage of the study will focus primarily on patients with melanoma, NSCLC, and RCC tumors since these tumor types exhibit higher expression levels of PD-L1, which are often associated with worse prognoses and have had RECIST v1.1 responses reported with PD-L1/PD-1 inhibitors. The dose-expansion stage of the study will also include other histologies that have been shown to express PD-L1 (e.g., head and neck cancers, esophageal cancer, gastric cancer, breast cancer, bladder cancer, prostate cancer, pancreatic cancer, endometrial cancer, GBM, HCC, CRC, malignant lymphoma, and multiple myeloma) in order to understand whether certain cancers have disease-specific safety signals. Eligibility criteria for both the dose-escalation and dose-expansion stages are based on safety data from nonclinical studies with atezolizumab and the nonclinical/clinical toxicity studies with other PD-L1 inhibitors.

3.2.2 Rationale for Starting Dose and Schedule with Phase I Material

The clinical starting dose and the associated safety factor were calculated based on results from the 8-week toxicology study in cynomolgus monkeys, which supported a NOAEL of 5 mg/kg (Study 08-1148). The clinical starting dose for this study will be 0.01 mg/kg administered to patients by IV infusion q3w. Results from Study 08-1148 provided a 268- to 160-fold safety factor on the basis of exposure and a BSA-normalized dose, respectively, thereby supporting a starting dose of 0.01 mg/kg in the selected Phase I clinical population with an adequate safety factor.

The dosing interval (every 21 days) is supported by PK evaluations and allows for a convenient integration with common chemotherapeutic regimens.

3.2.3 Rationale for the Dose-Escalation Scheme with Phase I Material

In the absence of DLTs, this study will evaluate approximately eight dose levels of atezolizumab in the dose-escalation portion of the study (0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 20 mg/kg given q3w). The proposed dose-escalation scheme is predicted to result in non-overlapping exposures in successive cohorts without subjecting patients to an excessive risk of toxicity. Additionally, the single-patient dose cohorts will evaluate non-target saturating dose levels of atezolizumab. Depending on new nonclinical efficacy, clinical safety, and PK data, additional intermediate dose levels and/or different schedules of atezolizumab may be evaluated.

3.2.4 Rationale for Dosing beyond Cycle 1

The toxicology program supports IV administration of atezolizumab to patients every week or less frequently for up to 8 weeks. Because the ethical conduct of a study of cancer therapy requires that patients have the opportunity to continue study treatment provided that the treatment is active and tolerable and that the patients comply with the requirements of the protocol, dosing beyond Cycle 1 for such patients will be allowed provided patients meet the rules to continue dosing beyond Cycle 1 as described in Section 3.1.1 and at the discretion of the investigator after a careful assessment and thorough discussion of the potential risks and benefits with the patient.

3.2.5 Rationale for the Dose-Limiting Toxicity Assessment Window

Toxicology studies in cynomolgus monkeys showed that atezolizumab was generally well tolerated following weekly dosing over an 8-week period. Therefore, the DLT assessment window of 21 days following the first dose of atezolizumab (representing one cycle of therapy in this study) is expected to allow for the adequate assessment of the nature and incidence of, as well as recovery from, acute toxicities related to atezolizumab.

3.2.6 Rationale for Expanding at or Below the Maximum Tolerated Dose or Maximum Administered Dose

Dose expansion at or below the MTD or MAD will be used to obtain additional safety, PK, PD, and efficacy data.

3.2.7 Rationale for the Pharmacokinetic Evaluation Schedule

A frequent sampling regimen is proposed to characterize the PK profile of atezolizumab in the dose-escalation portion of the study. This study is designed to adequately capture the distribution and elimination phases of atezolizumab and to allow the determination of maximum serum concentration (C_{max}), CL, V_{ss}, AUC, terminal half-life, and dose proportionality. Peak and trough serum concentrations will be determined at multiple cycles, which will allow the characterization of study treatment accumulation and the time to reach steady state.

PK information obtained from patients will be used to understand the relationship of dose to exposure and to support PK- or PK/PD–based dose selection for subsequent studies.

3.2.8 Rationale for Blood Sampling for Biomarkers

An exploratory objective is to evaluate changes in surrogate PD markers (T-cell subpopulations, and other exploratory biomarkers) in blood samples that are relevant because of the target expression. Assessment of changes in these factors may provide evidence for biological activity of atezolizumab in humans.

Limited data suggest that certain circulating PD markers (e.g., chemokine ligand ITAC) peak within 8–21 days after atezolizumab infusion. In order to define the PD profile of the early circulating biomarkers, which may be associated with immune-mediated adverse events, Cycle 1, Days 8 and 15 blood samples will be collected from the first 50 patients enrolled in the dose expansion cohorts after the implementation of Amendment 7.

In addition, potential correlations of these PD markers with the dose, safety, and anti-tumor activity of atezolizumab will be explored.

3.2.9 Rationale for the Collection of Archival Tumor Specimens

Development of a predictive diagnostic assay that enables prospective identification of patients who are likely to respond to treatment with atezolizumab may allow for a pre-selection of patients likely to benefit from treatment with this agent in future clinical studies. Preliminary results suggest that expression of PD-L1 by tumor cells correlates with response to anti–PD-1 therapy (Topalian et al. 2012). Archival paraffin-embedded tumor tissue will be used to assess PD-L1 expression by IHC and quantitative reverse-transcription polymerase chain reaction (qRT-PCR). In addition, other exploratory markers, such as potential predictive and prognostic markers that are related to PD-L1 activity, tumor immunobiology, or tumor type, may also be analyzed if guided by either nonclinical or clinical data. In consultation with the study investigators, prospective enrollment of PD–L1+ patients may be implemented.

3.2.10 Rationale for the Collection of Optional *Newly Collected* Tumor Specimens

The assessment of PD-L1/PD-1 pathway inhibition in tumor tissue would provide confirmation of the appropriate dose and exposure for atezolizumab for future studies. If both pre-treatment and *during* treatment serial tissue biopsy samples (e.g., at the time of response or progression) can be obtained with minimal risk and discomfort to patients, patients will be requested, via separate consent forms for the optional biopsy, to provide biopsy samples for the study of PD changes related to the activity of atezolizumab (changes in infiltration of CD8+ T cells and other exploratory biomarkers). Additionally, a limited number of patients may be enrolled in a dose-expansion cohort in which patients will undergo pre-treatment and *during* treatment serial biopsies.

3.2.11 Rationale for the Collection of Tumor Specimens at the Time of Initial Radiological Progression

Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed and can be preceded by initial apparent radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust tumor immune infiltration of the tumor with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional imaging (i.e., micrometastatic disease) may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010). In order to characterize the kinetics and biological basis of the potential anti-tumor activity of atezolizumab, all patients will undergo a mandatory tumor biopsy *tissue* sample collection, if clinically feasible, at the first evidence of early radiographic disease progression (i.e., not preceded by meaningful tumor regression).

3.2.12 Rationale for the Use of Immune-Related Response Criteria

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization) may not be sufficient to fully characterize the activity of immunotherapeutic agents. In studies with cytokines, cancer vaccines, and monoclonal antibodies, CR, partial response (PR), or SD have been shown to occur after an apparent increase in tumor burden as characterized by progressive disease with use of traditional response criteria. This initial increase in tumor burden in the setting of a T-cell response and potential delayed immunomodulated activity has been termed pseudoprogression (Hales et al. 2010). Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. The irRC (Wolchok et al. 2009) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). By irRC, patients may remain in the study with an increase in tumor burden $\geq$25% relative to nadir (immune-related progressive disease) in the absence of rapid clinical deterioration until progressive disease is confirmed by a repeat, consecutive assessment $\geq$4 weeks later. This study will employ both traditional RECIST v1.1 and irRC for tumor assessments in patients with solid malignancies. The 2007 Revised IWG and irRC and the IMWG Uniform Response Criteria with consecutive assessment $\geq$4 weeks after the initial response assessment will be used to analyze response for patients with malignant lymphoma and multiple myeloma, respectively. Given the proposed immunomodulatory mechanism of action of atezolizumab and the possibility of observing delayed responses, this will allow for the capture of a greater proportion of potential responses and allow patients to derive maximum clinical benefit. Patients must be withdrawn if they experience disease progression as described in Section 3.1.1. The use of traditional response criteria (e.g., RECIST v1.1, 2007 Revised IWG) in addition to irRC, as applicable, will ensure that all components of tumor burden are taken into consideration, including non-target and non-measurable disease.

3.2.13 Rationale for QT/QTc Assessment

The QT/QTc assessment strategy for this study is based on recommendations in the International Conference on Harmonisation (ICH) E14 guideline and is designed to focus on the collection of cardiac safety information that is most appropriate for a monoclonal antibody for cancer therapy in the Phase I setting. There are no concerns for cardiotoxicity on the basis of the mechanism of action, the nonclinical toxicology studies, or the limited clinical information available to date. The collection of 12-lead ECGs in triplicate via digital capture at the specified pharmacologically matched timepoints in the expansion cohorts will enable suitable collection of cardiac safety data and allow for an evaluation of the relationship between atezolizumab exposure and changes in QT/QTc interval.

3.2.14 Rationale for Atezolizumab Fixed Dosing with Phase III Material

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g as described below.

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and the observed atezolizumab interim pharmacokinetics in humans as well as other factors. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including: 95% tumor-receptor saturation is needed for efficacy and the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity and safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. 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, 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 associated with changes in pharmacokinetics for some patients in only 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 necessarily 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 the development of detectable ATAs does not appear to have a significant impact on the pharmacokinetics at doses of 10 to 20 mg/kg in most patients. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg 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 (or fixed-dose equivalent) for Phase II and III studies would be sufficient to

both maintain $C_{trough} \geq 6$ μg/mL and to 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 do not suggest any clinically meaningful differences in exposure following either a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected (equivalent to an average body weight–based dose of 15 mg/kg).

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of atezolizumab administered as a single-agent therapy for patients with locally advanced or metastatic solid tumors or hematologic malignancies will be assessed using the following primary safety outcome measures:

- Incidence and nature of DLTs
- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0

Additionally, safety will be assessed using the following secondary safety endpoints:

- Incidence of ATA response and the potential correlation with PK, PD, and safety parameters
- Changes in vital signs and ECG parameters
- Changes in clinical laboratory results
- Number of cycles and dose intensity

3.3.2 Pharmacokinetic Outcome Measures

The following PK data will be derived from the concentration-time data of atezolizumab when appropriate and when applicable:

- AUC
- C_{max}
- Minimum serum concentration (C_{min})
- CL
- V_{ss}

Other parameters, such as accumulation ratio, half-life, and dose proportionality, may also be calculated.

3.3.3 Activity Outcome Measures

The activity outcome measures are as follows:

- Best overall response rate with use of RECIST v1.1 and irRC for patients with solid malignancies (except for prostate cancer) and disease-specific criteria for patients with prostate cancer, GBM, malignant lymphoma and multiple myeloma (see Appendix 7, Appendix 8, Appendix 12, and Appendix 13)
- Objective response, defined as a CR or PR
- Duration of objective response, defined as time from the first occurrence of a documented objective response to the time of relapse or death from any cause
- Progression-free survival (PFS), defined as the time from the first study treatment to the first occurrence of progression or death, whichever occurs first

Objective response and disease progression will be determined using RECIST v1.1 (see Appendix 5) and irRC (see Appendix 6) for patients with solid malignancies (except for prostate cancer). Disease-specific criteria will be used to evaluate objective response and disease progression for patients with prostate cancer, GBM, malignant lymphoma or multiple myeloma (see Appendix 7,Appendix 8, Appendix 12, and Appendix 13).

3.3.4 Exploratory Outcome Measures

The following exploratory activity outcome measures will be assessed:

- Best overall response rate measured from Week 12 (i.e., excluding the Week 6 tumor assessment)
- OS, defined as the time from the first dose of atezolizumab to the time of death from any cause in the study

The following exploratory PD endpoints will be assessed when appropriate:

- Changes in various T-cell subpopulations in blood (e.g., effector/memory T cells, regulatory T cells, and other T-cell types)
- Identification and profiling of exploratory biomarkers in PBMCs (e.g., changes in expression of CD25 or human leukocyte antigen DR [HLA-DR], interferon [IFN]-γ production, and other markers)
- Changes in tumor-infiltrating, CD8+ T cells (and other exploratory markers) in *newly* obtained tumor tissue *samples* before and *during* atezolizumab treatment
- Identification and profiling of exploratory biomarkers in plasma (i.e., interleukin [IL]-2, IFN-γ, and other markers)
- Changes in tumor-infiltrating T-cell activity (measured by expression of granzyme B and other markers) in *newly* obtained tumor tissue prior to and during atezolizumab treatment

The following additional exploratory biomarker endpoints will be assessed when appropriate:

- Enumeration of CTCs in blood
- Status of PD-L1 (and other exploratory markers) in tumor tissue and in CTCs in blood

3.4 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). See Section 5 for complete details regarding safety reporting for this study.

Because this is the first time atezolizumab will be administered to humans, all patients will be monitored closely for toxicity. 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. Additionally, if the first three single-patient cohorts are expanded because of the occurrence of a DLT, dosing of patients in that cohort may be staggered by $\geq$24 hours depending on the nature of the DLT. Dosing of the first 3 patients enrolled in the first 3+3 cohort (0.3 mg/kg) only will be staggered by $\geq$24 hours. All adverse events and serious adverse events will be recorded during the study and for up to 90 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first. To mitigate potential unknown risks, at least in part, dosing beyond Cycle 1 will be limited to patients who have not developed unacceptable toxicity or had disease progression or who have evidence of potential pseudoprogression (see Section 4.6). The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

3.4.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. Whereas the MTD was not reached in a Phase I clinical study of an anti–PD-1 monoclonal antibody (BMS-936558) in patients with cancer, evidence of autoimmune conditions including pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis were reported (Topalian et al. 2012). Another Phase I clinical study of an anti–PD-L1 monoclonal antibody (BMS-936559) reported drug-related adverse events with potential immune-related causes including rash, hypothyroidism, hepatitis, adrenal insufficiency, sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis (Brahmer et al. 2012). As of 19 September 2013, adverse events with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, and pneumonitis, have been observed in Study PCD4989g. A more comprehensive list of observed adverse events is provided in Section 1.4.

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 guideline procedures for suspected immune-*related* adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

Cynomolgus monkeys receiving weekly IV or subcutaneous doses of anti–PD-L1 (atezolizumab) at 15 or 50 mg/kg in a repeat-dose toxicity study had histologic evidence of arteritis/periarteritis in medium-sized arteries. This finding is consistent with a known spontaneous condition in this species and may reflect an underlying predisposition to this autoimmune condition. Anti–PD-L1 therapy appears to have increased the incidence of this finding, which is compatible with the blocking of PD-L1 and the deregulation of peripheral tolerance. There were no apparent clinical sequelae of the arteritis in any of the animals. In addition, no toxicities were observed in cynomolgus monkeys that were given weekly IV doses of atezolizumab at 5 mg/kg (total nine doses). In an exploratory toxicology study in mice, findings attributed to atezolizumab were limited to minimal neuropathy of the sciatic nerve in C57Bl/6 mice at both doses tested (10 and 50 mg/kg). This observation is consistent with the observation that female PD-1–deficient mice develop autoimmune inflammation in multiple tissues, including peripheral nerves, whereas no such lesions were observed in age-matched PD-1–sufficient mice (Yoshida et al. 2008). No microscopic findings related to atezolizumab were observed in CD-1 mice, suggesting that this strain may not be predisposed to autoimmune inflammation under PD-L1 blockade.

In an exploratory research study, mortality was observed in mice acutely infected with clone 13 variant of lymphocytic choriomeningitis virus (LCMV CL-13) when a chimeric derivative of atezolizumab was administered. However, additional data in the LCMV CL-13 acute infection model suggest that this mortality is not unique to this chimeric antibody or the inhibition of the PD-L1/PD-1 pathway, because similar mortalities were observed with other PD-L1 and PD-1 inhibitors, as well as with IL-2 administration. Mortality was not observed in LCMV CL-13 chronically infected mice when a chimeric derivative of atezolizumab was administered. Additionally, PD-L1 blockade did not result in mortality in other models of acute viral infections (LCMV Armstrong, adenovirus, or vaccinia). These data suggest that the coincident broad tissue tropism, the high, sustained viral burden, and the large LCMV-specific T-cell response, features that distinguish LCMV CL13 from known human infections, may account for the mortalities observed in LCMV CL13. Because of the potential risks associated with infections, the Phase I study will exclude patients with a history of HIV, hepatitis B, or hepatitis C (except for patients with HCC co-infected with hepatitis B virus [HBV] or hepatitis C virus [HCV]) or with evidence of significant active infection. Atezolizumab dosing will also be withheld for new clinically significant infections and may resume if the infection resolves within 42 days. Despite these potential risks, it should

be noted that there is no reported evidence to date of an increased morbidity risk resulting from acute viral or bacterial infections in patients who have been treated with CT-011 or MDX-1106. There was no atezolizumab-dependent cytokine release detected following incubation with human PBMCs representing concentrations approximately 750-fold above the expected maximum observed concentration at the proposed starting dose, suggesting that the risk for exaggerated cytokine release associated with atezolizumab administration is low.

Refer to the Atezolizumab Investigator's Brochure for additional details regarding the nonclinical studies.

3.4.2 General Plan to Manage Safety Concerns

3.4.2.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies with atezolizumab as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors were taken into account (see Section 3.4.1).

3.4.2.2 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1 and Appendix 2. Patients will be followed for safety for 90 days following the last dose of study treatment or until receipt of another anti-cancer therapy, whichever comes first. The definitions of and response to DLTs have been designed to keep the degree and frequency of severe toxicity observed in this study within acceptable limits for Phase I studies in oncology.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1–Appendix 4 for the list and timing of study assessments). All serious adverse events and protocol-defined events of special interest (see Section 5.1.3) will be reported in an expedited fashion (see Section 5.4.2). In addition, the Medical Monitor and investigators will review and evaluate observed adverse events on a regular basis.

Patients who have an ongoing study treatment–related adverse event 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 anti-cancer 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 adverse event.

3.4.3 Management of Specific Safety Concerns

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 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, mycophenolate, or tumor necrosis factor alpha (TNF–α) inhibitors.

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

See the Atezolizumab Investigator's Brochure for details on management of GI, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic*, neurologic* or *potential* eye toxicity, and other immune-*related* adverse events.

3.4.3.1 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 when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

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

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

3.5 ETHICAL CONSIDERATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive atezolizumab treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.6.

3.6 ADMINISTRATIVE STRUCTURE

This study is sponsored by Genentech. Approximately 25 study centers in the United States and outside the United States will participate in this study. Patient dose assignment and drug supply will be managed through the use of an interactive voice/Web response system (IxRS). Data will be recorded via an electronic data capture (EDC) system from Medidata Solutions, Inc. (New York, NY), with use of electronic Case Report Forms (eCRFs; see Section 7.6). A central ECG facility will be used for ECG storage only. An ECG manual will be provided to study sites. Central laboratories will coordinate the collection of archival and *newly collected* pre-treatment and during treatment tumor tissue (as applicable) and of blood samples for the assessment of PK, PD, and predictive biomarkers.

3.7 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations, the ICH E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

4.1.1.1 General Inclusion Criteria

- Signed Informed Consent Form
- Age ≥ 18 years

  Adolescent patients who are 16–17 years old (body weight ≥ 40 kg) with one of the tumor types specified in this protocol would be considered for enrollment after discussion with and approval by the Medical Monitor.
- Histologically or cytologically documented, incurable or metastatic solid tumor or hematologic malignancy that is advanced (non-resectable) or recurrent and

progressing since the last anti-tumor therapy and for which no recognized standard curative therapy exists. Tumor type-specific criteria are detailed in Appendix 9.

For all sites, patients who have completed pre-screening tumor characterization and who have signed the pre-screening consent form may be considered for enrollment in the solid tumor or hematologic malignancy dose-expansion cohort on the basis of PD-L1 status. In the United States, this will apply only after submission of the IDI to the CDRH.

- Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, requested at any time prior to study entry. Only tissue from core needle, punch, or excisional biopsy sample collection will be accepted. Fine-needle aspiration, brushing, and lavage samples are not acceptable. For all biopsy types, submitted blocks should have sufficient tissue to generate at least 15 sections, and tissue for which the pathology report specifies that the overall tumor content is low (e.g., "sparse" or "scant") is not acceptable. Tissue from separate timepoints (such as time of initial diagnosis and time of metastatic diagnosis) or from the multiple metastatic tumors may also be collected for a given patient, on the basis of availability.

  For patients in the dose-expansion cohorts, archival tumor tissue must be confirmed to be available prior to study entry.

  If archival tissue is either insufficient or unavailable, the patient may still be eligible upon discussion with the Medical Monitor if the patient can provide at least five unstained, serial slides or is willing to consent to and undergo a pre-treatment core or excisional biopsy sample collection of the tumor. Fine-needle aspiration, brushing, and lavage samples are not acceptable.

  For patients with HCC, a core needle biopsy of the liver lesion is required during the screening period (archival tumor tissue could be submitted prior to the submission of *newly collected* tumor tissue).

- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):

  ANC $\geq$ 1500 cells/μL

  WBC counts $>$ 2500/μL

  Lymphocyte count $\geq$ 500/μL

  Platelet count $\geq$ 100,000/μL; for patients with hematologic malignancies, platelet count $\geq$ 75,000/μL

  Hemoglobin $\geq$ 9.0 g/dL

  Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

  Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

  AST and ALT $\leq 3.0 \times$ ULN with the following exception:

  Patients with liver involvement: AST and/or ALT $\leq 5 \times$ ULN

Alkaline phosphatase $\leq 2.5 \times$ ULN with the following exception:

Patients with documented liver involvement or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

If laboratory test values meet eligibility criteria during screening, but *do not meet the eligibility criteria* on Cycle 1, Day 1, the patient may still be eligible for treatment with Medical Monitor approval following a discussion with the investigator.

- Measurable disease per RECIST v1.1 (see Appendix 5) for patients with solid malignancies

  Disease-specific criteria will be used for patients with prostate cancer, GBM, malignant lymphoma, or multiple myeloma:

  Prostate cancer: measurable disease from progression defined by at least one of the following:

  Prostate-specific antigen (PSA) progression according to Prostate Cancer Working Group 2 (PCWG2) criteria: PSA level of at least 2 ng/mL which has subsequently risen on at least two successive occasions at least 2 weeks apart. If the second risen value is lower than the first risen value, then an additional test for rising PSA will be required to document progression. The value of the additional test must be higher than the first risen value (Scher et al. 2008).

  Radiographic progression in soft tissue or bone lesions

  GBM: bi-dimensionally measurable disease with a minimum measurement of 1 cm in one diameter on magnetic resonance imaging (MRI) performed within 14 days prior to first treatment (Day 0)

  Baseline MRIs for patients who underwent salvage surgery after first relapse must be obtained ≥ 4 weeks after the procedure. If receiving corticosteroids, patients must be on a stable or decreasing dose of corticosteroids for ≥ 5 days prior to baseline MRI.

  Malignant lymphoma: at least one bi-dimensionally measurable lesion measuring > 1.5 cm in its largest dimension by computed tomography (CT) scan

  Multiple myeloma: measurable disease defined by at least one of the following: monoclonal protein in the plasma of ≥ 1.0 g/dL; monoclonal protein in the urine of ≥ 0.2 g/24-hour urine collection; or serum Ig free light chain (FLC) ≥ 100 mg/L (10 mg/dL) and an abnormal serum immunoglobulin kappa to lambda FLC ratio

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate

of $<$1% per year during the treatment period and for at least $5\ months$ after the last dose of atezolizumab

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, established proper use of 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 study 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.

- ECOG performance status of 0 or 1 (see Appendix 7)

  Patients with ECOG performance status of 2, secondary to the underlying disease, may be enrolled after consultation with the Medical Monitor.

  Karnofsky Performance Status $\geq$70 for patients with GBM

- INR and aPTT $\leq 1.5 \times$ ULN

  This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low–molecular weight heparin or warfarin) should be *receiving* a stable dose.

4.1.1.2 Inclusion Criteria Unique to Patients Undergoing Serial Biopsy in the Serial Biopsy Dose-Expansion Cohort

- Baseline tumor tissue samples consisting of core needle biopsies for deep tumor tissue or organs or excisional or punch biopsies for cutaneous or subcutaneous lesions will be obtained. For cutaneous or subcutaneous lesions, tumors should be $\geq$ 5 mm in diameter amenable to serial biopsy by excisional or punch biopsies without unacceptable risk of a major procedural complication and at least two accessible lesions should be present (one for pre-treatment biopsy, one for *biopsy sample collection during* treatment). For core needle biopsy specimens, at least three cores should be submitted for evaluation. If more than one biopsy is planned to be taken from one lesion, the lesion must be large enough to permit successive biopsies $\geq$1 cm apart. An additional biopsy sample may be collected per investigator discretion, preferably at the time of radiographic progression or response.

4.1.2 Exclusion Criteria

4.1.2.1 General Exclusion Criteria

- Any approved anti-cancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:

Hormonal therapy with gonadotropin-releasing hormone (GnRH) agonists or antagonists for prostate cancer

Hormone-replacement therapy or oral contraceptives

Herbal therapy >1 week prior to Cycle 1, Day 1 (herbal therapy intended as anti-cancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)

Palliative radiotherapy for bone metastases >2 weeks prior to Cycle 1, Day 1

- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia
- Bisphosphonate therapy for symptomatic hypercalcemia

  Use of bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) is allowed.
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease
- Patients with acute leukemia, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma
- Known primary CNS malignancy or symptomatic CNS metastases (see Appendix 9 for disease-specific criteria for patients with GBM)

  Patients with asymptomatic untreated CNS disease may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:

  Evaluable or measurable disease outside the CNS

  No metastases to brain stem, midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)

  No history of intracranial hemorrhage or spinal cord hemorrhage

  No ongoing requirement for dexamethasone for CNS disease; patients *receiving* a stable dose of anticonvulsants are permitted

  No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1

  Patients with asymptomatic treated CNS metastases may be enrolled after consultation with the Medical Monitor, provided all the criteria listed above are met as well as the following:

  Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  No stereotactic radiation or whole-brain radiation within 28 days prior to Cycle 1, Day 1

Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to pharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Inability to comply with study and follow-up procedures
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune hypothyroidism *receiving* a stable dose of thyroid replacement hormone may be eligible.

  Patients with controlled Type 1 diabetes mellitus *receiving* a stable insulin regimen may be eligible.

  Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

  Patients with psoriasis must have a baseline ophthalmologic examination to rule out ocular manifestations

  Rash must cover less than 10% of 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 PUVA [psoralen plus ultraviolet A radiation], 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 CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory test result 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) *defined as having a positive hepatitis B surface antigen (HBsAg) test at screening* or hepatitis C infection *defined as having a positive HCV antibody test followed by a positive*

HCV RNA test at screening (see Appendix 9 for disease-specific criteria for patients with HCC)

Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

The HCV RNA test will be performed only for patients who have a positive HCV antibody test. Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Active tuberculosis
- Patients in dose-escalation cohorts: absence of Epstein-Barr virus (EBV) antibodies (negative EBV serology, negative Epstein-Barr nuclear antigen [EBNA] IgG)
- Severe infections within 4 weeks prior to Cycle 1, Day 1 including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients who are receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- 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 or anticipation that such a live attenuated vaccine will be required during the study *or within 5 months following the last dose of atezolizumab*

  Influenza vaccination should be given during influenza season only (approximately October *through* May *in the Northern Hemisphere and approximately April through September in the Southern Hemisphere*). Patients must *agree* not receive live, attenuated influenza vaccine (e.g., FluMist®) *28 days* prior to Cycle 1, Day 1*, during treatment,* or *within 5 months following the last dose of atezolizumab*.
- Malignancies other than disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., CLL Rai Stage 0, prostate cancer with Gleason score ≤6, and PSA ≤10 mg/mL, etc.)

4.1.2.2 Exclusion Criteria Related to Medications

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

  Patients who have received prior treatment with anti–CTLA-4 may be enrolled, provided the following requirements 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 (CTCAE Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including but not limited to IFN-α, IL-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF agents) within 2 weeks prior to Cycle 1, Day 1

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

  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

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. Patients will be assigned to dose levels in the order in which they are enrolled.

Once all required screening test results are available and eligibility has been confirmed, the study site will be required to fax or e-mail to Genentech information regarding the patient's eligibility for approval prior to enrollment.

Upon completion of all screening evaluations and verification that the patient has met all eligibility criteria, sites will obtain a patient number and cohort assignment and confirm the assigned dose through the IxRS.

4.3 STUDY TREATMENT

4.3.1 Formulation

Atezolizumab will be provided in the following configurations:

- The atezolizumab drug product produced using the Phase I manufacturing process is provided in a single-use, 2-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 1.2 mL (150 mg) of

atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 1.2 mL volume. The atezolizumab drug product is formulated as 125 mg/mL atezolizumab in 20 mM histidine acetate, 240 mM sucrose, 0.02% polysorbate 20, pH 5.5 (Phase I formulation).

- The atezolizumab drug product produced using the Phase III manufacturing process 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 (Phase III formulation).

The two formulations for the atezolizumab drug product are not to be used interchangeably during the study. In general, patients enrolled before the implementation of Amendment 6 will receive Phase I formulation throughout their course of treatment. Patients enrolled after the implementation of Amendment 6 will use Phase III formulation throughout their course of treatment. The guidelines regarding the assignment of study treatment formulations may be further modified on the basis of availability of the Phase I or Phase III formulation and will be communicated to the sites.

For further details, see the Atezolizumab Investigator's Brochure and Pharmacy Manual.

4.3.2 Dosage, Administration, and Storage

The dose levels of atezolizumab in the Phase I formulation tested in this study include 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 20 mg/kg administered by IV infusion q3w (21 [±2] days). Additional intermediate dose levels and/or different schedules of atezolizumab may be tested on the basis of new nonclinical efficacy, clinical safety, and clinical PK data at the time and after discussions with the investigators.
The atezolizumab dose will be based on the patient's weight (in kilograms) measured ≤14 days before baseline (Cycle 1, Day 1). It is not necessary to correct dosing on the basis of ideal body weight. For dose levels of 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg, doses will be prepared by diluting atezolizumab with diluent (formulation buffer) into an empty sterile vial. For dose levels ≥14 mg/kg, no dilution is required.

The dose level of atezolizumab in the Phase III formulation proposed 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 q3w (21 [±2] days).

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.

For more detailed information regarding administration, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥2 at the discretion of the treating physician after consultation with the Medical Monitor. The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, 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 infusion-related event (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 infusion-related event.
- For severe or life-threatening infusion-related events (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 infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix 11.

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. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.3.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Refer to the Atezolizumab Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

4.3.3 Dosage Modification

Intrapatient dose escalation up to the MAD will be allowed for patients in dose levels below the MAD who have SD or clinical benefit as assessed by investigator after completing four cycles of atezolizumab treatment, provided that the patients have not experienced a drug-related major toxicity and the Medical Monitor has approved the dose escalation. After intrapatient dose escalation, 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 4.6.

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days beyond the scheduled date of delayed infusion if study drug–related toxicity requiring dose suspension is experienced. If atezolizumab is withheld because of adverse events for $>$84 days beyond the scheduled date of infusion, then the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 5.2.1.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of $\leq$10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Any toxicity 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 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 there is no available antidote for atezolizumab. In severe cases, immune-related toxicity may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

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.

For management of treatment-related adverse events and immune-*related* adverse events, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual. See Section 4.3.2 for guidelines for the management of infusion-related reactions (see Appendix 11 for precautions for anaphylaxis).

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any medication *(e.g., prescription drugs,* over-the-counter *drugs, vaccines, herbal or homeopathic remedies, nutritional supplements)* used by a patient *from* 7 days preceding the screening evaluation and the treatment discontinuation visit. *All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.*

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; see Appendix 8).

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$2 at the discretion of the treating physician after consultation with the Medical Monitor. 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. Planned use of other medications should be discussed with the Medical Monitor.

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.2) may be used during the study at the discretion of the investigator.

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.2) may be used during the study at the discretion of the investigator.

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 randomization, during treatment or within 5 months following the last of atezolizumab but may receive inactivated vaccine.

Patients who use hormonal therapy with GnRH agonists or antagonists for prostate cancer, 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 4.1.2) should continue their use. Males and females of reproductive potential should use highly effective means of contraception. All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

4.4.2 Excluded Therapy

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

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 4.1.2 and 4.4.1)

  After Cycle 1, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases); atezolizumab administration may be suspended during radiotherapy with agreement from the Medical Monitor.

  Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Such cases must be discussed with and approved by the Medical Monitor.

- *Denosumab (a RANKL inhibitor) is prohibited during the atezolizumab treatment because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead during atezolizumab treatment.*

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited for patients with solid malignancies. For patients with hematologic malignancies, such medications may be allowed after discussion and approval from the Medical Monitor.

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

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

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

4.5 STUDY ASSESSMENTS

See Appendix 1–Appendix 4 *for the schedule of activities to be performed during the study*. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

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

4.5.1 Definitions of Study Assessments

4.5.1.1 Informed Consent Forms and Screening Log

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

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

4.5.1.2 Medical History *and Demographic Data*

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), prior cancer therapies and procedures, and all medications used by the

patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

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

4.5.1.3 Vital Signs

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

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

4.5.1.4 Physical Examination

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

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

As part of tumor assessments, a physical examination should also include the evaluation of the presence and degree of enlarged lymph nodes, skin neoplasm, hepatomegaly, and splenomegaly.

All patients should be monitored for symptoms of brain metastases. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological examination. A CT or MRI scan of the head should be done as clinically indicated to confirm or refute new or worsening brain involvement.

4.5.1.5 Tumor and Response Evaluation

Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. For solid malignancy patients with measurable disease, response will be assessed by the investigator per RECIST v1.1 (see Appendix 5), and irRC (see Appendix 6). For patients with prostate cancer, GBM, malignant lymphoma or multiple myeloma, response will be assessed using disease-specific criteria (see Appendix 7, Appendix 8, Appendix 12, and Appendix 13)

and irRC (see Appendix 6), as applicable. For patients actively on atezolizumab treatment, tumor assessments should be performed during the last week of the even cycles and before the start of treatment in the next cycle (see Appendix 1 and Appendix 2 for schedule). At the investigator's discretion, disease assessment (e.g., CT scans, MRI, or bone marrow biopsies) may be performed at any time if progressive disease is suspected.

Patients with Solid Malignancies

Screening assessments must include CT scans of the chest, abdomen, and pelvis (with oral/IV contrast unless contraindicated) and a brain scan (CT with IV contrast or MRI). A spiral CT scan of the chest may be obtained but is not a requirement. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological examination. A CT or MRI scan of the head should be done as clinically indicated to confirm or refute new or worsening brain involvement. For patients with HCC or with liver metastasis, a multiphasic MRI or CT scan of the liver should be performed.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment. If an ^{18}fluorodeoxyglucose (FDG)-PET imaging is performed, PET scans should be acquired 60–75 minutes after administration of the FDG imaging agent, at screening, and throughout the study, in a fasting patient ($>$4 hours prior to PET scan) with glucose $\leq$120 mg/dL. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 or irRC may be used.

For subsequent tumor assessments, procedures for tumor assessment should be performed as clinically indicated. The same imaging method used at screening must be used throughout the study. Stable brain metastases must be evaluated with each tumor assessment with the same radiographic procedure as at the baseline study. Patients without brain metastases do not need brain scans for tumor assessment unless clinically warranted.

Assessment of PSA levels should be performed with each tumor assessment and as clinically indicated for patients who have prostate cancer.

Assessment of cancer antigen 125 (CA125) levels should be performed with each tumor assessment and as clinically indicated for patients who have ovarian cancer.

Assessment of alfa-fetoprotein (AFP) levels should be performed with each tumor assessment and as clinically indicated for patients with HCC.

Patients with solid tumors who continue treatment beyond radiographic disease progression per RECIST v.1.1 will be monitored with a follow-up scan at the next

scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 12 weeks (see Appendix 1 and Appendix 2), the follow-up scan must be performed at 6 (±2) weeks as an unscheduled tumor assessment or earlier if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Patients with Prostate Cancer

Screening assessments must include CT scans of the chest, abdomen, and pelvis (with oral/IV contrast unless contraindicated) and a bone scan. Bone scans must be acquired using Tc99-MDP tracer. A brain scan (CT with IV contrast or MRI) is not required unless clinically indicated.

Bone scans are required to assess tumor progression in prostate patients by modified PCWG2 criteria. Therefore, if bone lesions are observed at baseline, then bone scans are to be done at same frequency as CT scans, at the time of the protocol-specified tumor assessment (i.e., every 6 or 12 weeks).

For patients who do not have bone lesions at baseline, bone scans will be initiated when the investigator feels that bone scans are clinically warranted. These should be done at the time of the protocol-specified tumor assessment. If bone lesions develop in the study, then bone scans should continue to be done at the same frequency as CT scans (i.e., every 6 or 12 weeks).

Assessment of PSA levels should be performed with each tumor assessment or as clinically indicated for patients who have prostate cancer.

Patients with prostate cancer who continue treatment beyond disease progression per Prostate Cancer Response Criteria will be monitored with a follow-up visit at the next scheduled tumor assessment when the tumor evaluation frequency is every 6 weeks or less. If the scan frequency is every 12 weeks (see Appendix 1 and Appendix 2), the follow-up tumor assessment must be performed at 6 (± 2) weeks as an unscheduled tumor assessment or earlier if clinically indicated. At the investigator's discretion, tumor evaluation may be repeated at any time if progressive disease is suspected.

Patients with GBM

An MRI of the brain at screening and with each tumor assessment should be used instead of a CT of the brain. CT scans of the chest, abdomen, and pelvis are not required. Assessment of the entire brain should be acquired using, at minimum, a 1.5T MRI scanner with each tumor assessment or as clinically indicated. The following images are required: axial T1 pre-Gd, axial T2 Fast Spin Echo, axial fluid attenuated inversion recovery (FLAIR), axial T1 post-Gd, and coronal T1 post-Gd.

Patients with GBM who continue treatment beyond disease progression per RANO Response Criteria will be monitored with a follow-up scan at the next scheduled tumor

assessment when the tumor evaluation frequency is every 6 weeks or less. If the tumor evaluation frequency is every 12 weeks (see Appendix 1 and Appendix 2), the follow-up tumor evaluation must be performed at 6 (±2) weeks as an unscheduled tumor assessment or earlier if clinically indicated. At the investigator's discretion, tumor evaluation may be repeated at any time if progressive disease is suspected.

An independent review of the responses of all patients with solid malignancies may be conducted, including a blinded review of MRI and/or CT scans at an independent review facility. All primary imaging data used for tumor assessment may be collected by the Sponsor to enable a centralized, independent review of response endpoints.

Patients with Malignant Lymphoma

Screening and follow-up tumor assessments must include CT scans of the chest, abdomen, and pelvis (with oral/IV contrast unless contraindicated). CT scans of the neck should be included if clinically indicated. If a CT scan of the neck is obtained during screening, then it should continue to be performed throughout the study. CT scans of the brain are not required. Assessment of B symptoms, LDH, and peripheral blood counts should be performed at screening and with each tumor assessment. Assessment of the bone marrow should include an evaluation of the bone marrow (i.e., trephine biopsy) for morphology and an aspirate and are required at screening and at Cycle 4, Days 15–21. If the bone marrow is involved at screening and still involved at Cycle 4, Days 15–21, a subsequent bone marrow examination is required only to confirm a CR.

Patients who continue treatment beyond radiographic disease progression per the 2007 Revised IWG Response Criteria for malignant lymphoma will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 12 weeks (see Appendix 1 and Appendix 2), the follow-up scan must be performed at 6 (±2) weeks as an unscheduled tumor assessment or earlier if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected.

Patients with Multiple Myeloma

Assessment of serum protein electrophoresis/immunofixation electrophoresis (SPEP/IFE), serum FLC, serum β-2 microglobulin, and peripheral blood counts should be performed at screening and with each tumor assessment. Urine protein electrophoresis/immunofixation electrophoresis (UPEP/IFE) from 24-hour urine collection should be performed at screening and with each tumor assessment only if positive at baseline. Assessment of the bone marrow (i.e., aspirate and trephine biopsy) will be required at screening, at Cycle 4, Days 15–21, and at any time needed to confirm a CR. A skeletal survey will be required at screening, at Cycle 4, Days 15–21, and at any time needed to confirm a CR. CT or MRI scans may also be included as needed for the measurement of soft tissue plasmacytomas.

Patients who continue treatment beyond radiographic disease progression per the 2006 Revised IMWG Response Criteria for multiple myeloma will be evaluated at a follow-up visit at the next scheduled tumor assessment when the tumor evaluation frequency is every 6 weeks. If the tumor evaluation frequency is every 12 weeks (see Appendix 1 and Appendix 2), the follow-up tumor evaluation must be performed at 6 (±2) weeks as an unscheduled tumor assessment or earlier if clinically indicated. At the investigator's discretion, tumor evaluations may be repeated at any time if progressive disease is suspected.

4.5.1.6 Laboratory Assessments

Samples for hematology, serum chemistries, coagulation, urinalysis, and the *serum* pregnancy test will be analyzed at the study site's local laboratory. Central laboratories will coordinate the collection of archival tumor, *newly collected* tumor, and leftover tumor tissue and blood samples for the assessment of atezolizumab pharmacokinetics and PD biomarkers, ATA assays, and auto-antibody testing. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (aPTT and INR)
- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, and free T4)
- HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen)

  HBV DNA test is required for any patients who have positive serology for anti-HBc and patients with HCC who have positive serology for HBsAg. *Consider consultation with a virologist to monitor for HBV reactivation.*
- HCV serology (anti-HCV)

  HCV RNA test is required for patients who have positive serology for anti-HCV
- Hepatitis D virus (HDV) serology (anti-HDV IgG)

  HDV serology is required only for patients with HCC who have positive serology for HBsAg
- PSA, CA125, and AFP (if applicable)

- SPEP/IFE, serum FLC, serum β-2 microglobulin, and UPEP/IFE from 24-hour urine collection (applicable to multiple myeloma patients only)

Instruction manuals and supply kits will be provided for all central laboratory assessments. The following assessments will be performed at a central laboratory or at Genentech:

- ATA assays

  Anti-atezolizumab antibody titers with use of validated immunoassays

- PK assays

  Serum atezolizumab concentration with use of validated assays

- Auto-antibody testing

  Anti-nuclear antibody

  Anti–double-stranded DNA

  Circulating anti-neutrophil cytoplasmic antibody

  Perinuclear anti-neutrophil cytoplasmic antibody

- Biomarker assays

  Blood samples will be obtained for biomarker evaluation from all eligible patients at the screening visit. Samples will be processed to obtain blood cells or plasma for the determination of changes in surrogate PD biomarkers. For all patients enrolled in the dose-escalation cohorts and for the first 10 patients enrolled in each expansion cohort, blood will also be obtained on Days 1 (before and after atezolizumab administration), 2, and 8 of Cycle 1; on Day 1 (before atezolizumab administration) of Cycles 2, 3, 4, 5, 7, 17, and 32; at the follow-up visit 30 days after the last dose of study treatment; and at the time of progression during the follow-up period for patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity).
  For additional patients enrolled in the expansion cohorts, blood will be obtained on Day 1 of Cycles 1, 2, 3, 4, 5, 7, and 32; at the follow-up visit 30 days after the last dose of study treatment; and at the time of progression during the follow-up period for patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity). For the first approximately 50 patients enrolled after implementation of Amendment 7, blood will be obtained on Days 8 and 15 of Cycle 1. A detailed blood sampling schedule is provided in Appendix 3 and Appendix 4.

Any remaining samples collected for PK, biomarker assays, and ATAs may be used for exploratory biomarker profiling, identification, and PD assay development purposes and additional safety assessments (e.g., ATA assay) as appropriate.

- Archival tumor tissue sample

  Archival tumor tissue samples obtained outside of this study for other purposes will be collected, if available, from all patients (paraffin blocks are preferred at least 15 unstained slides are acceptable). The tissue will be used for evaluating PD-L1 status by IHC and qRT-PCR.

  Other exploratory biomarkers might be also assessed if guided by clinical and nonclinical data. Tumor tissue samples will be stored indefinitely; assays on stored tissue samples may be performed at Genentech or at a central specialty laboratory.

  For patients in the dose-expansion cohorts, tumor tissue must be confirmed to be available prior to study entry.

- For patients in the dose-expansion cohort who are undergoing serial biopsies:

  Screening Biopsy
  Baseline tumor tissue samples consisting of core needle biopsies for deep tumor tissue or organs or excisional or punch biopsies for cutaneous or subcutaneous lesions will be obtained. Cutaneous or subcutaneous tumors $\geq$5 mm in diameter amenable to excisional or punch biopsies are required for the 10 patients in the dose-expansion cohort who will be undergoing sample collection for serial biopsies. If resection of cutaneous lesions is considered, a minimum of two accessible lesions should be present). Excisions should be made according to site-approved methods.

  If resections of whole lesions are not possible, punch biopsies of $\geq$5 mm in diameter should be taken.

  Note: If more than one biopsy is planned to be taken from one lesion, the lesion must be large enough to permit successive biopsies $\geq$1 cm apart.

  or

  Ideally, patients should have at least two accessible liver lesions amenable to core needle biopsies without unacceptable risk of a major procedural complication (one pre-treatment and at least one *during* treatment biopsy will be performed; minimum diameter, 18 gauge). Two or three lesions should be present, and if possible, successive passes should be $\geq$ 1 cm apart.
  At least 3 cores should be collected from each lesion.

  During Treatment Biopsy
  A subsequent biopsy will be performed approximately 2 weeks (Cycle 1, Day 15) following the first administration of atezolizumab.

  Note: The subsequent biopsy may be performed at approximately 1 week (Cycle 1, Day 8) following the first administration of atezolizumab if there is early sign of response (from physical examination, etc.) as determined by the investigator.

Biopsy at Time of Progression or Response
An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression (tumor biopsy at initial radiographic progression is mandatory) or response.

- For patients who agree to undergo biopsies by signing the Optional Informed Consent Form:

  Biopsies may be performed per investigator discretion, preferably at baseline, the time of early response (from physical examination, etc.), or the time of radiographic progression (especially when pseudoprogression is suspected) or response.

  Tumor tissue samples can be collected using core needle, punch, excisional biopsy (as specified above), or forceps biopsy. Fine-needle aspiration, brushing, and lavage samples are not recommended.

  If a patient undergoes a medically indicated procedure (i.e., bronchoscopy, esophagogastroduodenoscopy, colonoscopy, etc.) any time during the course of the study that has the likelihood of yielding tumor tissue, any remaining samples or a portion of the sample not necessary for medical diagnosis (body fluid samples or leftover tumor tissue) may be obtained for exploratory analysis. Patients must have provided specific consent in the Optional Research Informed Consent Form in order for discarded samples from routine care to be obtained.

- Tumor biopsy at the time of initial radiographic progression

  All patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible, at the first evidence of early radiographic disease progression (i.e., not preceded by meaningful tumor regression).

  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. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

- For patients with HCC:

  Mandatory Screening Biopsy
  Baseline tumor tissue sample from the liver will be obtained using core needle biopsy.

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

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

4.5.1.7 Electrocardiograms

For patients in the dose-escalation cohorts, 12-lead ECGs are required as part of the screening assessment; 30 (±15) minutes before and after infusion on Day 1 of Cycle 1; 30 (±15) minutes before and after infusion on Day 1 of Cycles 2, 3, and 4; and at the treatment discontinuation visit.

For patients in the dose-expansion cohorts, digitized, triplicate ECGs will be performed. Resting 12-lead ECGs are required as part of the screening assessment, 30 (±15) minutes before and after infusion on Day 1 of Cycle 1, 30 (±15) minutes before infusion on Day 1 of Cycle 4, and at the treatment discontinuation visit. A central facility will be used for storage of ECGs from patients in the dose-expansion cohorts. An ECG manual will be provided to study sites.

ECGs will be reviewed by the investigator to determine patient eligibility at screening, as well as suitability for continued treatment during the study.

If QTc prolongation (>500 ms) is noted, the ECG should be repeated hourly with time-matched PK samples (within 30 minutes of the ECG) until prolongation is reversed or stabilized. The cause of the QTc prolongation (e.g., electrolyte imbalance) should be evaluated and the Medical Monitor should be notified.

To minimize postural variability, it is important that patients be resting and in a supine position for at least 10 minutes prior to ECG collection. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability due to the effects of physiologic stress.

4.5.1.8 Anti-Therapeutic Antibody Testing

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see Appendix 3 and Appendix 4 for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.

4.5.2 Assessments during Screening and after Confirmation of Eligibility

All screening evaluations must be completed and reviewed by the investigator and the Medical Monitor to confirm that patients meet all eligibility criteria before the first infusion of study treatment. Written informed consent for participation in the study must be

obtained before performing any study-specific screening tests or procedures. Prior to signing the full consent form for the study, patients may be given the option of signing a pre-screening consent form to specifically allow for the collection of archival tumor tissue. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

See the study flowcharts provided in Appendix 1 and Appendix 2 for the schedule of screening and pre-treatment assessments. Screening and pre-treatment tests and evaluations will be performed within 28 days preceding Cycle 1, Day 1 (defined as the day of the first dose of study treatment) unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window may be used; such tests do not need to be repeated for screening. Screening local laboratory assessments obtained ≤96 hours prior to Cycle 1, Day 1 do not have to be repeated for Cycle 1, Day 1.

Archival tumor tissue samples obtained outside this study will be collected, if available, from all patients. For patients in the dose-expansion cohorts, archival tumor tissue must be confirmed to be available prior to study entry.

Blood samples will be obtained for biomarker evaluation from all eligible patients at the screening visit (see Appendix 1–Appendix 4).

The following will be obtained from patients who are either in the dose-expansion cohort requiring serial biopsies or who have signed the Optional Research Informed Consent Form:

- Pre-treatment and *during* treatment *newly collected* tumor tissue
- Body fluid samples or leftover tumor tissue from non–study-related procedures

4.5.3 Assessments during Treatment

All visits must occur within ±1 day from the scheduled date unless otherwise noted (see Appendix 1 and Appendix 2). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

See the study flowcharts provided in Appendix 1–Appendix 4 for the schedule of treatment period assessments. If the first three single-patient cohorts are expanded because of the occurrence of a DLT, dosing of patients in that cohort may be staggered by ≥24 hours depending on the nature of the DLT. Dosing of the first 3 patients enrolled in the first 3+3 cohort (0.3 mg/kg) only will be staggered by ≥24 hours.

The following assessments may be performed ≤96 hours before Day 1 of each cycle: ECOG performance status, limited physical examination, and local laboratory tests.

If scheduled dosing is precluded because of a holiday, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 2 days, the patient can resume the original schedule. If scheduled study assessments cannot be obtained because of a holiday, these assessments should then be obtained at the soonest following date, provided that the soonest following date is not within 2 days of other regularly scheduled study assessments.

After five cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

Blood samples for PD biomarker analysis and pharmacokinetics will be obtained according to the schedules in Appendix 3 and Appendix 4.

During treatment *newly collected* tumor biopsy samples will be obtained from patients who have signed the Optional Research Informed Consent Forms and for patients who are in the dose-expansion cohort requiring serial biopsies.

The following will be obtained from patients who provided specific consent in the Optional Research Informed Consent Form:

- Body fluid samples or leftover tumor tissue for additional research (samples from medically indicated procedures may be obtained and sent at any time during the study)

4.5.4 Treatment Discontinuation Visit

Patients who discontinue from treatment will be asked to return to the clinic not 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.

See the study flowcharts provided in Appendix 1–Appendix 4 for assessments to be performed at the treatment discontinuation visit.

4.5.5 Follow-Up Assessments

4.5.5.1 Ongoing Tumor Assessments

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until the patient dies, experiences disease progression, withdraws consent, or initiates further systemic cancer therapy or until the study closes, whichever occurs first.

In order to allow for more flexibility for patients who do not clinically require frequent scans, tumor assessments for patients that have discontinued treatment but remain in

*active follow up should be performed **at least** every 6 months, but may be done more frequently as clinically indicated per discretion of the investigator.*

4.5.5.2 Adverse Events

After the treatment discontinuation visit, all adverse events (including serious adverse events [see Section 5.1.2] and protocol-defined events of special interest [see Section 5.1.3]), regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer 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 adverse event.

4.5.5.3 Survival Follow-up

Following treatment discontinuation, all patients will be followed for survival. Survival follow-up information will be collected via clinic visits, telephone calls, and/or review of patient medical records approximately every 3 months until patient death, loss to follow-up, withdrawal of consent, or until the study is terminated by the Sponsor.

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

4.5.5.4 ATA and PK Assessments

ATA and PK samples are to be obtained every 30 (± 14) days for up to 120 days after the last dose of study treatment unless the patients withdraw consent, or the study closes, whichever occurs first. ATA and PK samples collected at the treatment discontinuation visit will be counted as the first collection.

Please see the study flowcharts provided in Appendix 1 and Appendix 2 for specified follow-up assessments.

4.6 PATIENT, *TREATMENT, STUDY, AND SITE* DISCONTINUATION

4.6.1 *Patient and Study Treatment 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 or Sponsor determines may jeopardize the patient's safety if he or she continues in the study*
- *Investigator or Sponsor determines it is in the best interest of the patient*

Any patient who withdraws will be encouraged to return to the study center for a follow-up visit. Patients who discontinue treatment should return within 30 days of discontinuation (see Section 4.5.4). *Every effort should be made to obtain information on patients who withdraw from the study.* The primary reason for discontinuation must be recorded on the appropriate eCRF. *However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will be replaced.*

Patients must be withdrawn from the study if they experience any of the following:

- Disease progression by: RECIST v1.1 and irRC in patients with solid malignancies; both RANO Response Criteria and irRC in patients with GBM; both 2007 Revised IWG Response Criteria and irRC in patients with malignant lymphoma; Prostate Cancer Response Criteria and repeat assessment; and both the IMWG Uniform Response Criteria and repeat assessment ≥4 weeks after the initial response evaluation in patients with multiple myeloma:

  Patients who demonstrate radiographic disease progression per RECIST v1.1 for solid tumors; per RANO Response Criteria for GBM that has not been confirmed by irRC; per 2007 Revised IWG Response Criteria for malignant lymphoma that has not been confirmed by irRC; per Prostate Cancer Response Criteria that has not been confirmed by repeat assessment; or per IMWG Uniform Response Criteria for multiple myeloma that has not been confirmed by repeat assessment may be considered for continued study treatment if they meet all of the following criteria:

  Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease

  No decline in ECOG performance status

  Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

  Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

  Patients who demonstrate confirmed radiographic disease progression according to: both RECIST v1.1 and irRC (solid tumors); both the 2007 Revised IWG Response Criteria and irRC (malignant lymphoma); both the IMWG Uniform Response Criteria and repeat assessment ≥4 weeks after the initial response evaluation (multiple myeloma); both RANO Response Criteria and irRC (GBM); or both the Prostate Cancer Response Criteria and repeat assessment ≥3 weeks after the initial response evaluation (prostate cancer) may be considered for continued study treatment at the discretion of the investigator following discussion with the Medical Monitor, provided they continue to meet all the criteria above and have evidence of clinical benefit.

- Intolerability to atezolizumab, including development of an immune-*related* adverse event determined by the investigator and Medical Monitor to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Experienced a DLT
- Pregnancy

Other reasons for patient discontinuation may include but are not limited to the following:

- Change in patient eligibility
- Noncompliance
- Patient decision

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study and for reasons of non-compliance (e.g., missed doses, visits) or if the investigator determines it is in the best interest of the patient. Patients who become pregnant must be withdrawn from the study (see Section 5.3.1 for pregnancy reporting instructions).

See the study flowchart in Appendix 1–Appendix 4 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

4.6.2 Study *and Site* Discontinuation

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 adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor 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 ICH guideline for GCP*
- *No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)*

4.7 POST-STUDY ACCESS

*Currently, the Sponsor (*Genentech*, a member of the Roche Group)* does not *have any plans* to provide atezolizumab or other study interventions to patients *who have completed* the study or any earlier withdrawal. *The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:*

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.8 ASSAY METHODS

- Atezolizumab PK assay: atezolizumab concentration in serum will be determined using a validated ELISA method.
- Anti-atezolizumab antibody assay: serum samples will be evaluated for anti-atezolizumab antibodies with use of a validated bridging antibody immunoassay.
- Biomarker assays: blood samples for biomarker assessments will be assayed using analytically qualified methods such as modified ELISA (or equivalent), Luminex, and fluorescence-activated cell sorting (FACS). Tumor samples for biomarker assessment will be assayed using IHC, quantitative PCR, sequencing, and reverse-phase protein array platforms.

4.9 DATA QUALITY ASSURANCE

Genentech will be responsible for data management of this study, including quality checking of the data. The data will be collected via EDC with use of eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, Genentech will request data clarification from the sites, which the sites will resolve electronically in the EDC system. Genentech will produce an EDC study specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to Genentech with use of Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech, and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events*, including* serious adverse events *and adverse events of special interest*, *performing* protocol-specified *laboratory assessments,* measur*ing* protocol-specified vital signs; and *conducting* other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

Genentech or its designee is responsible for reporting relevant serious adverse events to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Genentech or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Genentech or its designee will report other relevant serious adverse events associated with the use of the study treatment to the appropriate competent authorities (according to local guidelines), investigators, and central Institutional Review Boards/Ethics Committees (IRBs/ECs) (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 Adverse Events

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

This includes the following:

- Adverse events not previously observed in the patient that emerge during the protocol-specified adverse event reporting period, including signs or symptoms associated with locally advanced or metastatic cancer that were not present prior to the adverse event reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- Adverse events that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, medication washout, or no treatment run-in)
- Preexisting medical conditions (other than locally advanced or metastatic cancer) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified adverse event reporting period

5.1.2 Serious Adverse Events

A serious adverse event is any adverse event that *meets* any of the following *criteria*:

- *Is f*atal (i.e., the adverse event actually causes or leads to death)
- *Is l*ife threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization *(see Section 5.3.1.8)*
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- *Is a* congenital anomaly/birth defect in a neonate/infant born to a mother exposed to *study drug*
- *Is* a significant medical event *in* the investigator*'s judgement* (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (*e.g., rated* as mild, moderate, or severe*, or according to NCI CTCAE*); the event itself may be of relatively minor medical significance (such as severe headache *without any further findings*).

Severity and seriousness *need to* be independently assessed *for each* adverse event *recorded* on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.1.3 Protocol-Defined Events of Special Interest

The following events are events of special interest and will need to be reported to the Sponsor expeditiously (see Section 5.4 for reporting instructions) irrespective of regulatory seriousness criteria. Specific guidelines for protocol-defined events of special interest by NCI CTCAE grade are provided below:

- Conditions suggestive of an autoimmune disorder including but not limited to hepatitis, pneumonitis, colitis, endocrinopathies, thyroiditis, colitis, rheumatoid arthritis, diabetes, vasculitis, neuritis, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, vitiligo, dermatitis, iritis, etc.
- Grade $\geq$3 acute infection (bacterial, viral, zoonotic, or fungal)
- Grade $\geq$3 events suggestive of hypersensitivity, cytokine release, systemic inflammatory response, or infusion reaction syndromes including but not limited to fever, chills, rash, urticaria, dyspnea, wheezing, angioedema, tachycardia, hypotension, etc.
- Grade $\geq$2 rash or pruritus
- Grade $\geq$2 diarrhea
- Grade $\geq$3 AST/ALT/total bilirubin elevation—asymptomatic
- Grade $\geq$2 AST/ALT/total bilirubin elevation—with constitutional symptoms

- Grade ≥2 hypoxia or dyspnea

5.1.4 Dose-Limiting Toxicities

Adverse events that meet the definition of a DLT (see Section 3.1.1) will be recorded on the Adverse Event eCRF. In addition, a written DLT Assessment Worksheet should be completed and submitted immediately to the Medical Monitor as described in Section 5.4.3. If a DLT also meets the definition of a serious adverse event or a protocol-defined event of special interest, the event will also qualify for expedited reporting to the Sponsor (see Sections 5.4.1 and 5.4.2 for reporting instructions). Investigators will also participate in frequent teleconferences with the Sponsor during which they will report any DLTs observed during the DLT assessment window for each patient in the dose-escalation stage of the study.

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events and serious adverse events (as defined in Section 5.1) are recorded on the *Adverse Event* eCRF and reported to the Sponsor in accordance with protocol instructions.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality.

5.2.1 Adverse Event Reporting Period

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

After informed consent but prior to the initiation of study drug, only serious adverse events caused by a protocol-mandated intervention will be collected (e.g., serious adverse events related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of the study drug, all adverse events and serious adverse events regardless of attribution will be collected until 90 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anti-cancer therapy, whichever occurs first. Patients will be contacted at 60 and 90 days after the last dose of study treatment to determine if any new adverse events have occurred. After this period, investigators should report only serious adverse events that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Events

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

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

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

5.2.3 Assessment of Severity and Causality of Adverse Events

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

For each adverse event and serious adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity, and causality.

Table 1 provides guidance for grading adverse event severity and Table 2 provides guidance for assessing the causal relationship to atezolizumab.

The adverse event grading (severity) scale found in NCI CTCAE v4.0 will be used for assessing adverse event severity (see Table 1).

Table 1 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL [b]
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [c]
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event	

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Notes: The NCI CTCAE v4.0 can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Regardless of severity, some events may also meet regulatory seriousness criteria. Refer to definition of a serious adverse event (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported adverse event is not in the NCI CTCAE listing.

[b] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

To ensure consistency of causality assessments, investigators should apply the general guidelines outlined in Table 2.

Table 2 Causal Attribution Guidance

Is the adverse event/serious adverse event suspected to be caused by the investigational product (atezolizumab) on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the investigational product, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the investigational product; and/or the adverse event abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge. **Investigators should apply facts, evidence, or rationales on the basis of scientific principles and clinical judgment to support a causal/contributory association with an investigational product. This should include any events that could be considered definitely, probably, or possibly related to study drug.**
NO	**Adverse events will be considered related unless they fulfill the criteria as specified below.** Evidence exists that the adverse event has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug). **Investigators should apply facts, evidence, or rationales based on scientific principles and clinical judgment to support that such an event is not related to study drug.** Note: The investigator's assessment of causality for individual adverse event reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual adverse event reports, the Sponsor will promptly evaluate all reported serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities. **Attribution of serious adverse events will be reviewed on an ongoing basis and may be changed as additional clinical data emerge (e.g., reversibility of adverse event, new clinical findings in patient with adverse event, adverse events in other patients)**.

In addition to assessing causality with respect to study drug, investigators should also assess whether other factors (e.g., disease under study, concurrent illness, concomitant medication, or study procedure) may have caused the event, using similar guidance.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording adverse events or serious adverse events on the eCRF and avoid the use of colloquialisms and abbreviations.

There is one Adverse Event eCRF for recording adverse events or serious adverse events.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

5.3.1.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the 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 non-serious signs and/or symptoms cannot be medically characterized as a single non-serious diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate adverse event on the eCRF. If a constellation of serious signs and/or symptoms cannot be medically characterized as a single serious diagnosis or syndrome at the time of reporting, one serious adverse event should be reported on the adverse event eCRF with the most medically significant sign or symptom as the primary event term. The additional signs and symptoms should be captured in the Additional Case Details section of the adverse event eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information and the event term should be updated to reflect the medical diagnosis.

Symptoms that occur during or within 24 hours after an atezolizumab infusion and may be part of an acute infusion reaction should not be recorded under the diagnosis of "infusion-related reaction." Rather, non-serious symptoms should be recorded as separate adverse events on the adverse event eCRF. Serious symptoms should be reported as one serious adverse event on the adverse event eCRF with the most medically significant sign or symptom as the primary event term. Additional signs and symptoms should be reported in the Additional Case Details section of the adverse event eCRF. This type of reporting is to enable detailed analyses of acute infusion-related symptoms in relation to atezolizumab dose, atezolizumab regimen, and given premedication.

5.3.1.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an adverse event or serious adverse event on the eCRF.

However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe GI hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

5.3.1.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution between patient evaluation timepoints. Such events should be recorded only once in the eCRF unless their severity increases. If a persistent adverse event becomes more severe, it should be recorded again on an Adverse Event eCRF. If the adverse event becomes serious, it should then be recorded as a serious adverse event. If the severity of a previously reported serious adverse event changes, it should be reported as follow-up to the previous serious adverse event and not as a new event.

A recurrent adverse event is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent adverse events should be recorded on an Adverse Event eCRF.

5.3.1.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as adverse events or serious adverse events on the eCRF (e.g., abnormalities that require discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an adverse event or serious adverse event on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the adverse event or serious adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as adverse events or serious adverse events on the eCRF unless their severity, seriousness, or etiology changes.

5.3.1.5 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.2.1), regardless of attribution, will be recorded on an Adverse Event eCRF and expeditiously reported to the Sponsor. This includes death attributed to progression of cancer.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the Adverse Event eCRF.

If the death is attributed to progression of cancer, record “Cancer Progression” as the serious adverse event term on the Adverse Event eCRF.

5.3.1.6 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event or serious adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.1.7 Worsening of Cancer

Worsening and/or progression of cancer should not be recorded as an adverse event or serious adverse event, with the exception of deaths due to progression of cancer (see Section 5.3.1). These data will be captured as efficacy assessment data only.

5.3.1.8 Hospitalization, Prolonged Hospitalization, or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as a serious adverse event when there is no occurrence of an adverse event. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

5.3.1.9 Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of investigational product, a Pregnancy Report eCRF should be completed and submitted via the EDC system to Genentech’s Drug Safety Department or its designee within 24 hours of learning of the pregnancy.

Abortion, should always be classified as serious (because the Sponsor considers these medically significant), recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor. After the study period, such events should be reported expeditiously to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be classified as serious, recorded on an Adverse Event eCRF, and expeditiously reported to the Sponsor. After the study period, such events should be reported expeditiously to the Sponsor recorded and reported as a serious adverse event.

In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to Genentech's Drug Safety Department or its designee at the fax numbers listed in Section 5.4.2.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST

5.4.1 Reporting Requirements for Fatal/Life-Threatening Serious Adverse Events Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal adverse event that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an Adverse Event eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information in the United States:

Medical Monitor:	Redacted
Telephone No.:	Redacted
Alternate Telephone No.:	Redacted
For sites outside the United States:	Country-specific contact information will be supplied to sites.

5.4.2 Reporting Requirements for All Serious Adverse Events and Protocol-Defined Events of Special Interest

Investigators will submit reports of all serious adverse events, regardless of attribution, and all protocol-defined events of special interest to Genentech within 24 hours after learning of the events. For initial serious adverse event and protocol-defined events of special interest reports, investigators should record all case details that can be gathered within 24 hours on an Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Genentech Drug Safety by the EDC system. In the event the EDC system is unavailable, a completed serious adverse event or Serious/Non-serious Expedited Adverse Event paper reporting form and fax coversheet should be faxed immediately upon completion to Genentech's Drug Safety Department or its designee at the fax numbers indicated below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

For all sites in the United States:
Fax No.: Redacted
Alternate Fax No.: Redacted

For sites outside the United States: Country-specific contact information will be supplied to sites.

5.4.3 Reporting Requirements for Dose-Limiting Toxicities

For DLTs occurring during the DLT assessment window, sites will complete a DLT Assessment Worksheet and include any supporting documentation (e.g., physical examination notes, adverse event source documents, copy of completed adverse event eCRFs, laboratory reports) and fax them within 48 hours after observing or learning of the event to the Genentech Medical Monitor at (866) 228-8617. The Medical Monitor will review the worksheet.

DLTs should also be reported on the adverse event eCRF as adverse events or serious adverse events as appropriate.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved adverse events and serious adverse events until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the adverse event/serious adverse event. Resolution of adverse events and (with dates) should be documented on the appropriate Adverse Event eCRF and in the patient's medical record to facilitate source data verification during the study period.

For some serious adverse events, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the serious adverse event report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent serious adverse events that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other serious adverse event occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Genentech Drug Safety on the study Adverse Event eCRF. If the study Adverse Event eCRF is no longer available, the

investigator should report the event directly to Genentech Drug Safety via phone at (888) 835-2555.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final analysis will be based on patient data collected through study discontinuation. The analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of atezolizumab. In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. All summaries will be presented by the assigned dose level or tumor type, when appropriate.

6.1 DETERMINATION OF SAMPLE SIZE

The dose-escalation stage sample size for this study is based on the dose-escalation rules described in Section 3.1.1.

Design considerations were not made with regard to explicit power and type I error considerations but were made to obtain preliminary safety, PK, and PD information in this patient population. The planned enrollment for this study is approximately 656–689 patients, depending on the number and size of the cohorts. The study will enroll approximately 21–54 patients in the dose-escalation stage and approximately up to 635 patients in the dose-expansion stage. Within each indication (e.g., RCC, melanoma, NSCLC) of the expansion cohort, the following rule will apply: if no responders (CR or PR) are observed from the first 14 patients who are considered to be more likely to respond on the basis of the presence of biomarkers potentially predictive of anti-tumor activity, enrollment will be suspended for that indication. With the assumption of a true response rate of 20% or higher, there is at most a 4.4% chance of not observing any response in 14 patients.

With an observed response rate of 30%, a sample size of 40 patients within a given indication (i.e., RCC, NSCLC) will result in a 90% CI of 19.96%–42.87%. The corresponding 90% CI with 20 patients will be 16.39%–48.38%.

Any patient who does not complete the DLT assessment window for any reason other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD assessment and will be replaced by an additional patient at that same dose level.

Table 3 describes the probability of not observing any DLTs in 1 patient, the probability of not observing any DLTs in 3 patients, and the probability of observing fewer than two DLTs in 6 patients for different underlying DLT rates during the dose-escalation stage.

Table 3 Probability of Observing DLTs for Different Underlying DLT Rates

Underlying DLT Rate	Probability of Observing No DLTs in 3 Patients	Probability of Observing Fewer Than Two DLTs in 6 Patients
0.10	0.73	0.89
0.20	0.51	0.66
0.33	0.30	0.36
0.40	0.22	0.23
0.50	0.13	0.11
0.60	0.06	0.04

DLT = dose-limiting toxicity.

To better characterize the safety of the single-agent MTD identified in the dose-escalation stage, additional expansion cohorts of approximately 40 patients (in RCC and NSCLC) will be enrolled. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in a given cohort of 6 patients is 47%, 26%, and 5.8%, respectively. The corresponding probabilities of observing at least one such adverse event in an expanded cohort of 40 patients will increase to 98.5%, 87.1%, and 33.1%, respectively.

6.2 ANALYSIS OF THE CONDUCT OF THE STUDY

Enrollment criteria exceptions, major protocol violations, study treatment administration, and reasons for patient discontinuations from the study will be described and summarized.

6.3 ANALYSIS OF TREATMENT AT BASELINE

Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, and baseline ECOG performance status, will be summarized.

6.4 SAFETY ANALYSES

Safety will be assessed through summaries of DLTs, adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to atezolizumab. All patients who receive any amount of atezolizumab will be included in the safety analyses.

Verbatim descriptions of adverse events will be mapped to thesaurus terms. Adverse event data will be listed by study site, dose cohort, treatment arm, patient number, and study day. Events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. In addition, serious adverse events, including deaths, will be listed separately and summarized.

Adverse events leading to treatment discontinuation will be listed. Adverse events leading to the declaration of DLTs will be listed. Patients who withdraw from the study prior to completing the DLT assessment window (Day 21) for reasons other than a DLT will be considered unevaluable for DLT and MTD assessments.

Relevant laboratory and vital signs data will be displayed by time, with NCI CTCAE Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by grade with use of NCI CTCAE v4.0.

Incidence of ATA response and the potential correlation with PK, PD, and safety parameters may be assessed.

6.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Individual and mean serum atezolizumab concentration versus time data will be tabulated and plotted by dose level. The pharmacokinetics of atezolizumab will be summarized by estimating total AUC, C_{max}, C_{min}, total CL, V_{ss}, and terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and coefficient of variation). Interpatient variability and drug accumulation will be evaluated.

PD analyses will include assessments of PD biomarkers in both tumor tissue and blood. Changes in PD and potential predictive biomarkers will be listed by dose, cohort, and response status. Additional PK and PD analyses will be conducted as appropriate.

6.6 ACTIVITY ANALYSES

The analyses described below will be conducted on the basis of responses as assessed by both RECIST v1.1 (see Appendix 5) and irRC (see Appendix 6) in patients with solid malignancies; both RANO Response Criteria (see Appendix 8) and irRC (see Appendix 6) in patients with GBM; by both 2007 Revised IWG Criteria (see Appendix 12) and irRC (see Appendix 6) in patients with malignant lymphoma; Prostate Cancer Response Criteria (see Appendix 7) and repeat assessment $\geq$3 weeks after the initial response evaluation in patients with prostate cancer; and as assessed by IMWG Uniform Criteria (see Appendix 13) with consecutive assessment $\geq$4 weeks later in patients with multiple myeloma.

Response assessment data, duration of objective response (for responders), and PFS will be listed for all patients with measurable disease by dose level or tumor type, when appropriate.

Objective response is defined as a CR or PR, as determined by investigator assessment and confirmed by repeat assessment $\geq$4 weeks after initial documentation (confirmation not required for patients with malignant lymphoma). Patients with missing or no response assessments will be classified as non-responders.

Objective response rate will be estimated and summarized by tumor type for the expansion cohorts.

Among patients with an objective response, duration of objective response will be defined as the time from the initial complete or partial response to the time of disease progression or death, whichever occurs first. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment.

PFS is defined as the time from the first day of study treatment with atezolizumab (Cycle 1, Day 1) until documented disease progression or death, whichever occurs first. For patients who do not have documented progressive disease or death before the end of the study, PFS will be censored at the day of the last tumor assessment.

Summaries will be provided for best overall response rate.

For the evaluation of OS, Kaplan-Meier methodology will be used to estimate the median OS and to construct survival curves. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each tumor type.

7. INVESTIGATOR REQUIREMENTS

7.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Genentech or a Genentech representative:

- FDA Form 1572 for each site (for all studies conducted under U.S. IND regulations), signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  Genentech or its designee must review any proposed deviations from the sample Informed Consent Form.

- Current laboratory certification of the laboratory performing the analysis (if other than a Genentech-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator's Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator

7.2 STUDY COMPLETION

The following data and materials are required by Genentech before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (if other than Genentech-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s)
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

7.3 INFORMED CONSENT FORM

Genentech's sample Informed Consent Form will be provided to each site. Genentech or its designee must review and approve any proposed deviations from the sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the consent forms during their participation in the study. The final IRB/EC-approved consent forms must be provided to Genentech for regulatory purposes.

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

All signed and dated consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised consent forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised consent form for continued participation in the study. The final revised IRB/EC–approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/EC review and approval may not be required per study site policies.

7.3.1 Optional Research Informed Consent

If obtaining pre-treatment and *during* treatment biopsy samples and remaining samples of tumor tissue for optional research described in Section 3.2.10 and Section 4.5.1 is approved by the IRB/EC, the consent form entitled "Sample Research Informed Consent Form" will be provided by Genentech to each study site. This form gives patients the option to authorize the collection and use of these samples and personal health information for additional research purposes. Signing of this separate consent form is not required for enrollment in the study but is required prior to any optional research sample collection. All procedures outlined above for review, approval, processing, and use of consent forms also apply to this optional research form.

In the United States, each Informed Consent Form may also include authorization allowing the institution, investigator, subinvestigator and the Sponsor(s) to use and disclose Personal Health information in compliance with the HIPAA of 1996.

Signed and dated Informed Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

7.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined adverse events to the Sponsor, investigators are required to promptly report to their respective IRBs/ECs all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all serious adverse events, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's study file.

7.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Genentech representative to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit Genentech monitors/representatives and collaborators, the FDA, other regulatory agencies, IRBs, and the respective national or local health authorities to inspect facilities and records relevant to this study.

7.6 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the EDC system. Sites will receive training and a manual for appropriate eCRF completion. eCRFs will be submitted electronically to Genentech and should be handled in accordance with instructions from Genentech.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

7.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification (SDV) to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical study.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

7.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals, (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file), (3) protects the database from tampering, and (4) ensures data preservation.

In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

7.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug in IxRS indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

7.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (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 monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

7.11 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 this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator 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.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States 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.

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Appendix 1
Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

	Screening [a]	Cycle 1					Cycles ≥2			Cycles ≥2	Treatment Discon. Visit [b]	Follow-Up
Assessment Window (days)	Days –28 to –1	*Day* 1	*Day* 2	*Day* 4 or 5 [c]	*Day* 8	*Day* 15 (±1)	*Day* 1 [d] (±2)	*Day* 8 (±2)	*Day* 15 (±2)	*Days* 15–21	≤30 Days after Last Dose	
Signed Informed Consent Form(s) [a]	x											
Review of eligibility criteria	x											
Medical, surgical, and cancer histories, including demographic information [e]	x											
EBV, HBV, HCV serology [f]	x											
Concomitant medications [g]	x	x			x	x	x	x [h]	x [h]		x	
Tumor assessment [i]	x									Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy		
CA125, AFP, or PSA assessment [j]	x									Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy		
Complete physical examination [k]	x										x	
Limited physical examination [k]		x [l]			x	x	x [l]			x		
ECOG performance status	x	x [l]					x [l]				x	

Appendix 1
Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

	Screening [a]	Cycle 1					Cycles ≥ 2			Cycles ≥ 2	Treatment Discon. Visit [b]	Follow-Up
Assessment Window (days)	Days –28 to –1	*Day* 1	*Day* 2	*Day* 4 or 5 [c]	*Day* 8	*Day* 15 (±1)	*Day* 1 [d] (±2)	*Day* 8 (±2)	*Day* 15 (±2)	*Days* 15–21	≤ 30 Days after Last Dose	
Vital signs [m]	x	x			x	x	x				x	
12-lead ECG [n]	x	x					x [n]				x	
Weight	x [l]	x					x				x	
Height	x											
Local laboratory assessments												
Hematology [o]	x	x [l]	x		x	x	x [l]	x [h]	x [h]		x	
Serum chemistry [p]	x	x [l]	x		x	x	x [l]	x [h]	x [h]		x	
Coagulation panel (aPTT, INR)	x										x	
Urinalysis [q]	x						x [r]				x	
Serum pregnancy test [s]	x											
TSH, free T3, free T4 [t]	x										x	
Auto-antibody testing [u]	x						x [r]				x	
Serum sample for ATA assessment [v]		x					x [v]				x	x
Serum sample for PK sampling [w]		x	x	x [c]	x	x	x [w]				x	x
Plasma and blood sample for PD biomarkers [x]	x	x	x		x		x [x]				x	x

Appendix 1
Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

	Screening [a]	Cycle 1					Cycles ≥ 2			Cycles ≥ 2	Treatment Discon. Visit [b]	Follow-Up
Assessment Window (days)	Days –28 to –1	*Day* 1	*Day* 2	*Day* 4 or 5 [c]	*Day* 8	*Day* 15 (±1)	*Day* 1 [d] (±2)	*Day* 8 (±2)	*Day* 15 (±2)	*Days* 15–21	≤ 30 Days after Last Dose	
Adverse events		x	x	x [c]	x	x	x	x [h]	x [h]		x	x
Study treatment infusion [y]		x					x					
Archival tumor tissue specimen or 15 unstained slides [z]	x											
Newly collected tumor specimen [aa]	x					x				x		x
Survival follow-up [bb]												x

AFP = alpha-fetoprotein; ATA = anti-therapeutic antibody; CA = cancer antigen; CT = computed tomography; Discon = discontinuation; DLT = dose-limiting toxicity; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; FDG = ^{18}fluorodeoxyglucose; HBV = hepatitis B virus; HCC = HCV = hepatitis C virus; irRC = immune-related Response Criteria; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate-specific antigen; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent can be obtained up to 30 days prior to study entry and is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose for a treatment discontinuation visit. After this visit, all adverse events (including serious adverse events and protocol-defined events of special interest), regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Patients will be contacted at 60 and 90 days after the last dose of study treatment to determine whether any new adverse events have occurred. Ongoing

Appendix 1
Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event.

[c] For patients in the dose-escalation cohorts only.

[d] On Day 1 of Cycle 2, infusion of atezolizumab can be administered only after completion of the 21-day DLT assessment window, which has a window of +2 days (but not −2 days). All subsequent Day 1 infusions can be administered with a window of ±2 days.

[e] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age, sex, and self-reported race/ethnicity.

[f] *Patients with past or resolved HBV infection (negative HBsAg, positive anti-HBc antibody) should be referred to a virologist to monitor for HBV reactivation.*

[g] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications, or medications used since the last documentation of medications will be recorded.

[h] Day 8 of Cycles 2, 3, and 4 only and Day 15 of Cycle 2 only.

[i] Examinations performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at this visit, with use of physical examination and image-based evaluation. For patients with solid malignancies, screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment. If an FDG-PET imaging is performed, PET scans should be acquired 60–75 minutes after administration of the FDG imaging agent at screening and throughout the study, in a fasting patient (>4 hours prior to PET scan) with glucose ≤120 mg/dL. Disease status will be assessed using RECIST v1.1 and irRC. Other methods of assessment of measurable disease according to RECIST v1.1 or irRC may be used. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results have to be reviewed by the investigator before dosing at the next cycle. For patients with other malignancies, refer to Section 4.5.1. Tumor assessments will be performed every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy. Patients who continue study treatment beyond disease progression should continue to undergo scheduled tumor assessments approximately every 12 weeks until treatment discontinuation.

[j] PSA level for patients with prostate cancer, CA125 levels for patients with ovarian cancer, AFP for patients with HCC, or other tumor marker

Appendix 1
Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

(as appropriate) should be obtained as clinically indicated or with each tumor assessment.

[k] Complete and limited physical examinations are defined in Section 4.5.1.

[l] ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤96 hours before Day 1 of each cycle.

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

[n] For patients in the dose-escalation cohorts, 12-lead ECGs are required as part of the screening assessment, 30 (±15) minutes before and after infusion on Day 1 of Cycle 1; 30 (± 15) minutes before and after infusion on Day 1 of Cycles 2, 3, and 4; and at the treatment discontinuation visit. For patients in the dose-expansion cohorts, digitized, triplicate, 12-lead ECGs will be obtained as part of the screening assessment, 30 (± 15) minutes before and after infusion on Day 1 of Cycle 1, 30 (± 15) minutes before infusion on Day 1 of Cycle 4, and at the treatment discontinuation visit. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[o] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[p] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[q] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[r] On Day 1 of Cycle 3 and every two cycles thereafter.

[s] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1.

[t] *Monitoring should occur every 4 cycles (12 weeks).*

[u] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[v] See Appendix 3 for details of the ATA collection schedule.

Appendix 1
Study Flowchart: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

[w] See Appendix 3 for detailed PK sampling schedule; blood samples should be processed to obtain serum.

[x] See Appendix 3 for details of the PD sampling schedule.

[y] The initial dose of study treatment will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, 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.

[z] Archival tumor tissue specimen may be obtained from any prior tumor excision or biopsy performed at any time during the course of the patient's illness. Patients may choose to sign a pre-screening consent form to enable the collection of tumor samples for ≥28 days prior to Day 1 of Cycle 1.

[aa] Tumor tissue will be obtained by core needle or excisional/punch biopsy from patients who have signed the Optional Research Informed Consent Form. Tumor tissue will also be obtained by excisional/punch/core needle biopsy from patients who are undergoing serial biopsies in the dose-expansion cohort. The predose specimen will be obtained during the screening period. If the predose specimen is evaluable, a subsequent biopsy will then be performed approximately 2 weeks (Cycle 1, Day 15) after first atezolizumab administration. (The subsequent biopsy may be performed at approximately 1 week [Cycle 1, Day 8] following the first administration of atezolizumab if there is early sign of response as determined by the investigator.) An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response. See Section 4.5.1 for further details.

[bb] Survival follow-up information will be collected via clinic visits, telephone calls, and/or review of patient medical records approximately every 3 months until patient death, loss to follow-up, or until the study is terminated by the Sponsor. All patients will be followed for survival 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 the study, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts

Assessment Window (days)	Screening [a] Days –28 to –1	All Cycles *Day* 1 (±2)	All Cycles *Days* 15–21	Treatment Discon. Visit [b] ≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s) [a]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information [c]	x				
Concomitant medications [d]	x	X		x	
Tumor assessment [e]	x		Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death or initiation of further systemic cancer therapy		
Bone marrow examination (malignant lymphoma and multiple myeloma only) [f]	x		x		
SPEP/IFE, serum FLC, serum β-2 microglobulin (multiple myeloma only) [g]	x		x		
UPEP/IFE from 24-hour urine (multiple myeloma only) [g]	x		x		
Skeletal survey (multiple myeloma only) [h]	x		x		
CA125, AFP, or PSA assessment [i]	x		Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death or initiation of further systemic cancer therapy		
Complete physical examination [j]	x			x	
Limited physical examination [j]		x [k]			
ECOG or Karnofsky performance status	x	x [k]		x	
Vital signs [l]	x	X		x	

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts (cont.)

Assessment Window (days)	Screening [a] Days –28 to –1	All Cycles *Day* 1 (±2)	All Cycles *Days* 15–21	Treatment Discon. Visit [b] ≤30 Days after Last Dose	Follow-Up
Triplicate 12-lead ECG [m]	x	X		x	
B symptoms (malignant lymphoma only)	x		x	x	
Weight	x [n]	X		x	
Height	x				
Local laboratory assessments					
Hematology [n]	x	x [k]		x	
Serum chemistry [o]	x	x [k]		x	
Coagulation panel (aPTT, INR)	x			x	
Urinalysis [p]	x	x [q]		x	
Serum pregnancy test [r]	x				
TSH, free T3, free T4 [s]	x			x	
HBV, HCV, and HDV serology [t]	x				
HBV DNA or HCV RNA test [u]	x	x		x	
Central laboratory assessments					
Auto-antibody testing [v]	x	x [q]		x	
Serum sample for ATA assessment [w]		x [w]		x	x
Serum sample for PK sampling [x]		x [x]		x	x
Plasma and blood sample for PD biomarkers [y]	x	x [y]		x	x
Serum sample for quantitative HBsAg [z]		X		x	

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts (cont.)

Assessment Window (days)	Screening [a] Days –28 to –1	All Cycles *Day* 1 (±2)	All Cycles *Days* 15–21	Treatment Discon. Visit [b] ≤30 Days after Last Dose	Follow-Up
Adverse events		x [aa]		x	x
Study treatment infusion [bb]		X			
Archival tumor tissue specimen or 15 unstained slides [cc]	x				
Newly collected tumor specimen [dd]	x	x	x		x
Survival follow-up [ee]					x

AFP = alpha-fetoprotein; anti-HBc = antibody to hepatitis B core antigen; ATA = anti-therapeutic antibody; CA = cancer antigen; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FDG = ^{18}fluorodeoxyglucose; FLC = free light chain; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDV = hepatitis D virus; irRC = immune-related Response Criteria; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate-specific antigen; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SPEP/IFE = serum protein electrophoresis/immunofixation electrophoresis;TSH = thyroid-stimulating hormone; UPEP/IFE = urine protein electrophoresis/immunofixation.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent can be obtained up to 30 days prior to study entry and is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose for a treatment discontinuation visit. After this visit, all adverse events (including serious adverse events and protocol-defined events of special interest), regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Patients will be contacted at 60 and 90 days after the last dose of study treatment to determine if any new adverse events have occurred. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts (cont.)

grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event.

[c] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age, sex, and self-reported race/ethnicity.

[d] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[e] Examinations and biopsies performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at this visit, with use of physical examination and image-based evaluation. For patients with solid malignancies, screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment. If an FDG-PET imaging is performed, PET scans should be acquired 60–75 minutes after administration of the FDG imaging agent at screening and throughout the study, in a fasting patient (>4 hours prior to PET scan) with glucose ≤120 mg/dL. Disease status will be assessed using RECIST v1.1 and irRC. Other methods of assessment of measurable disease according to RECIST v1.1 or irRC may be used. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results have to be reviewed by the investigator before dosing at the next cycle. For patients with other malignancies, refer to Section 4.5.1. Tumor assessments will be performed every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy. Patients who continue study treatment should continue to undergo scheduled tumor assessments approximately every 12 weeks until treatment discontinuation. *Bone scans are required to assess tumor progression in prostate patients by modified PCWG2 criteria. Therefore, if bone lesions are observed at baseline, then bone scans are to be done at same frequency as CT scans, at the time of the protocol-specified tumor assessment (i.e., every 6 or 12 weeks). For patients who do not have bone lesions at baseline, bone scans will be initiated when the investigator feels that bone scans are clinically warranted. These should be done at the time of the protocol-specified tumor assessment. If bone lesions develop in the study, then bone scans should continue to be done at the same frequency as CT scans (i.e., every 6 or 12 weeks).*

[f] A bone marrow examination (aspirate and trephine biopsy) must be performed at screening for patients with malignant lymphoma and multiple myeloma. A repeat aspirate and biopsy at Cycle 4, Days 15–21 are also required to assess response. In patients with malignant lymphoma or multiple myeloma, a repeat bone marrow biopsy and aspirate are necessary to confirm a complete clinical response if physical examination and CT scan demonstrate a clinical response.

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts (cont.)

[g] For multiple myeloma patients, SPEP/IFE, serum FLC, serum β-2 microglobulin, and UPEP/IFE from 24-hour urine will be performed at screening and with each tumor assessment timepoint (i.e., end of Cycles 2, 4, 6, 8, 12, 16, 20, 24, 28, and 32 or as clinically indicated).

[h] For multiple myeloma patients, skeletal survey (a set of full body X-rays) will be performed at screening, Cycle 4, Days 15–21, and at any time needed to confirm complete response. CT or MRI scans may also be included as needed for the measurement of soft tissue plasmacytomas.

[i] PSA level for patients with prostate cancer, CA125 level for patients with ovarian cancer, AFP for patients with HCC, or other tumor marker (as appropriate) should be obtained as clinically indicated and with each tumor assessment.

[j] Complete and limited physical examinations are defined in Section 4.5.1.

[k] ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤96 hours before Day 1 of each cycle.

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

[m] For patients in the dose-expansion cohorts, digitized, triplicate, 12-lead ECGs will be obtained as part of the screening assessment, 30 (±15) minutes before and after infusion on Day 1 of Cycle 1, 30 (±15) minutes before infusion on Day 1 of Cycle 4, and at the treatment discontinuation visit. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[n] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[o] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[p] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[q] On Day 1 of Cycle 3 and every two cycles thereafter.

[r] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1.

[s] *Monitoring should occur every 4 cycles (12 weeks).*

[t] HDV serology at screening is required only for patients with HCC infected with HBV.

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts (cont.)

[u] HBV DNA test is required before Cycle 1, Day 1 for all patients who have positive serology for anti-HBc at screening. HBV DNA test at Day 1 of each cycle and treatment discontinuation visit is required for patients with HCC with positive HBsAg at screening. HCV RNA test is required before Cycle 1, Day 1 for non-HCC patients who have positive serology for anti-HCV at screening. HCV RNA test at Day 1 of each cycle and treatment discontinuation visit is required for patients with HCC with positive anti-HCV at screening. *Patients with past or resolved HBV infection (negative HBsAg, positive anti-HBc antibody) should be referred to a virologist to monitor for HBV reactivation.*

[v] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[w] See Appendix 4 for details of the ATA collection schedule.

[x] See Appendix 4 for detailed PK sampling schedule; blood samples should be processed to obtain serum.

[y] See Appendix 4 for details of the PD sampling schedule.

[z] Quantitative HBsAg will be assessed at a central laboratory in serum of patients with HCC who have a positive HBsAg at screening, at Day 1 of each cycle, and at the treatment discontinuation visit.

[aa] Adverse events will be checked additionally at Cycle 1, Day 1 and Cycle 1, Day 8 for the first approximately 50 patients enrolled into the dose expansion cohorts after the implementation of Amendment 7.

[bb] The initial dose of study treatment will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, 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.

[cc] Archival tumor tissue specimen may be obtained from any prior tumor excision or biopsy performed at any time during the course of the patient's illness. Patients may choose to sign a pre-screening consent form to enable the collection of tumor samples for ≥28 days prior to Day 1 of Cycle 1.

[dd] Tumor tissue will be obtained by core needle or excisional/punch biopsy from patients who have signed the Optional Research Informed Consent Form. Tumor tissue will also be obtained by excisional/punch/core needle biopsy for patients who are undergoing serial biopsies in the dose-expansion cohort. The predose specimen will be obtained during the screening period. If the predose specimen is evaluable, a subsequent biopsy will then be performed approximately 2 weeks (Cycle 1, Day 15) after the first atezolizumab administration. (The subsequent biopsy may be performed at approximately 1 week [Cycle 1, Day 8] following the first administration of atezolizumab if there is early sign of response as determined by the investigator.) An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response. See Section 4.5.1 for further details.

[ee] Survival follow-up information will be collected via clinic visits, telephone calls, and/or review of patient medical records approximately every 3 months until patient death, loss to follow-up, or until the study is terminated by the Sponsor. All patients will be followed for

Appendix 2
Study Flowchart: All Patients Except the First 10 Patients with Melanoma, RCC, or NSCLC in the Expansion Cohorts (cont.)

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

Appendix 3
Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

Study Visit	Time	Sample	
		Dose-Escalation Cohorts	Expansion Cohorts
Screening	At visit	Atezolizumab PD [a]	Atezolizumab PD [a]
Cycle 1, Day 1	Predose	ATA Atezolizumab PK Atezolizumab PD [a]	ATA Atezolizumab PK Atezolizumab PD [a]
	30 (±10) min after end of atezolizumab infusion	Atezolizumab PK Atezolizumab PD [b]	Atezolizumab PK Atezolizumab PD [b]
Cycle 1, Day 2	24 (±6) hr after end of atezolizumab infusion on Day 1	Atezolizumab PK Atezolizumab PD [b]	Atezolizumab PK Atezolizumab PD [b]
Cycle 1, Day 4	72 (±12) hr after end of atezolizumab infusion on Day 1	Atezolizumab PK	Not Applicable
Cycle 1, Day 8 (±1 day) [c]	At visit	Atezolizumab PK Atezolizumab PD [b]	Atezolizumab PK Atezolizumab PD [b]
Cycle 1, Day 15 (±1 day) [c]	At visit	Atezolizumab PK	Atezolizumab PK
Cycles 2, 3, 4, 5, and 7, Day 1 (±2 days)	Predose	ATA (Cycles 2 and 4 only) Atezolizumab PK [d] Atezolizumab PD [e]	ATA (Cycles 2 and 4 only) Atezolizumab PK [d] Atezolizumab PD [e]
	30 (±10) min after end of atezolizumab infusion	Atezolizumab PK [d]	Atezolizumab PK (Cycles 2, 3, and 4 only) [d]
Cycles 8, 10,12, 14, and 16, Day 1 (±2 days)	Predose	ATA (Cycles 8 and 16 only) Atezolizumab PK [d]	ATA (Cycles 8 and 16 only) Atezolizumab PK (Cycles 8 and 16 only) [d]
Cycles ≥7, Day 1 (±2 days)	Predose	Atezolizumab PK [f]	Atezolizumab PK [f]

Appendix 3
Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

Study Visit	Time	Sample	
		Dose-Escalation Cohorts	Expansion Cohorts
		ATA [f] Atezolizumab PD (Cycles 17 and 32 only) [g]	ATA [f] Atezolizumab PD (Cycles 17 and 32 only) [g]
Treatment discontinuation visit	At visit	ATA Atezolizumab PK Atezolizumab PD [a]	ATA Atezolizumab PK Atezolizumab PD [a]
Post–treatment discontinuation visits [h, i]	At visit	ATA Atezolizumab PK Atezolizumab PD [a, i]	ATA Atezolizumab PK Atezolizumab PD [a, i]
At time of *newly collected* biopsy (pre-treatment and on-treatment or at progression)	At visit	Atezolizumab PD [a]	Atezolizumab PD [a]

ATA = anti-therapeutic antibody; NSCLC = non–small cell lung cancer; PBMC = plasma or peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; RCC = renal cell carcinoma.

[a] Plasma and PBMCs.

[b] Plasma only.

[c] For the first approximately 50 patients enrolled after implementation of Amendment 7 only.

[d] In patients who undergo intrapatient dose escalation after Cycle 4 (i.e., starting with Cycle 5, Day 1), PK samples should also be obtained before dosing and 30 (± 10) minutes after end of atezolizumab infusion at Cycles 6 and 8.

[e] Cycles 2 and 3: plasma and PBMCs. Cycles 4 and 7: plasma. Cycle 5: PBMCs.

[f] *Cycles 17 and 20 and every eight cycles thereafter*

[g] *Plasma and PBMCs.*

[h] For patients who discontinue the study treatment, ATA and PK samples are to be obtained every 30 (± 14) days for up to 120 days after the last dose

Appendix 3
Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Patients in Dose-Escalation Cohorts and First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

of study treatment unless the patient dies or withdraws consent or the study closes. ATA and PK samples collected at the treatment discontinuation visit will be counted as the first collection.

[i] For patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) and continue to undergo scheduled tumor assessments approximately every 12 weeks. PD samples are to be obtained at disease progression if determined from follow-up tumor assessment.

Appendix 4
Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Except the First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts

Study Visit	Time	Sample
Screening	At visit	Atezolizumab PD [a]
Cycle 1, Day 1	Predose	ATA Atezolizumab PK Atezolizumab PD [a]
	30 (±10) min after end of atezolizumab infusion	Atezolizumab PK Atezolizumab PD [b]
Cycle 1, Days 8 and 15 (±1 day) [c]	At visit	Atezolizumab PD [a]
Cycles 2, 3, 4, 5, and 7, Day 1 (±2 days)	Predose	ATA (Cycles 2 and 4 only) Atezolizumab PK [d] Atezolizumab PD [e]
	30 (±10) min after end of atezolizumab infusion	Atezolizumab PK (Cycles 2, 3, and 4 only) [d]
Cycles 8, 10,12, 14,16, Day 1 (± 2 days)	Predose	ATA (Cycles 8 and 16 only) Atezolizumab PK [d]
Cycles ≥17, Day 1 (±2 days)	Predose	Atezolizumab PK (Cycles 17 and 20 and every eight cycles thereafter) ATA (Cycles 17 and 20 and every eight cycles thereafter) Atezolizumab PD (Cycles 17 and 32 only) [f]

Appendix 4
Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Except the First 10 Patients with Melanoma, RCC, or NSCLC in Expansion Cohorts (cont.)

Study Visit	Time	Sample
Treatment discontinuation visit	At visit	ATA Atezolizumab PK Atezolizumab PD [a]
Post–treatment discontinuation visits [g, h]	At visit	ATA Atezolizumab PK Atezolizumab PD [a, g]
At time of *newly collected* biopsy (pre-treatment and on-treatment or at progression)	At visit	Atezolizumab PD [a]

ATA = anti-therapeutic antibody; NSCLC = non–small cell lung cancer; PBMC = plasma or peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; RCC = renal cell carcinoma.

[a] Plasma and PBMCs.

[b] Plasma only.

[c] For the first approximately 50 patients enrolled after implementation of Amendment 7 only.

[d] In patients who undergo intrapatient dose escalation after Cycle 4 (i.e., starting with Cycle 5, Day 1), PK samples should also be obtained before dosing and 30 (± 10) minutes after end of atezolizumab infusion at Cycles 6 and 8.

[e] Cycles 2 and 3: plasma and PBMCs. Cycles 4 and 7: plasma. Cycle 5: PBMCs.

[f] Plasma and PBMCs

[g] For patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) and continue to undergo scheduled tumor assessments approximately every 12 weeks, PD samples are to be obtained at disease progression if determined from follow-up tumor assessment.

[h] For patients who discontinue the study, ATA and PK samples are to be obtained every 30 (± 14) days for up to 120 days after the last dose of study treatment unless the patient dies or withdraws consent or the study closes. ATA and PK samples collected at the treatment discontinuation visit will be counted as the first collection.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a. Measurable Tumor Lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

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

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

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

b. Method of Assessment

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

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

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

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

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

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study (nadir), including baseline

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

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum in the study

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

b. Special Notes on the Assessment of Target Lesions

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

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

<u>To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.</u>

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be

measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

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

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

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

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

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria

to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

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

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

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

Evaluation of Response

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing

lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

Appendix 5
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

"symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1–Table 3.

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

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 6
Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_{i} \text{(Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i)}.$$

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

Appendix 6
Immune-Related Response Criteria (cont.)

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden $\geq 50\%$ relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden $\geq 25\%$ relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 7
Prostate Response Evaluation Criteria

PROSTATE-SPECIFIC ANTIGEN ASSESSMENT

Prostate-specific antigen (PSA) Assessment will be evaluated according to the recommendations of the Prostate Cancer Working Group 2 (PCWG2)1 with modification.

- PSA complete response is defined as a PSA concentration <0.5 ng/mL for two consecutive measurements separated by at least 3 weeks.
- PSA response will be defined as a PSA concentration $<50\%$ of the PSA reference value occurring at any time after treatment is initiated. The PSA reference value will be the PSA concentration measured immediately prior to treatment.
- PSA decrease of $\geq 30\%$ from baseline by Week 12 will also be assessed.
- PSA progression is defined as follows:

  In patients where no decrease in PSA from baseline is documented, PSA progression is a $\geq 25\%$ increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment. It should be confirmed by a second value obtained 3 or more weeks later.

  In patients whose PSA nadir is $<$ 100% of the baseline value, PSA progression is$\geq 25\%$ increase from the nadir and an absolute increase of 2 ng/mL or more from the nadir, confirmed by a second value obtained 3 or more weeks later.

RADIOGRAPHIC ASSESSMENT

- Bone lesions

  Progression is defined as the appearance of two or more new lesions.

  Progression should be confirmed by a repeat measurement at least 6 weeks later demonstrating additional new lesions.

Please refer to the Prostate guidance in the Appendix II of the CRF Completion Guidelines for additional information on how to assess progression of bone lesions and evaluate tumor response according to modified Prostate Cancer Working Group 2 (PCWG2) criteria.

- Soft tissue lesions

  Soft tissue lesions should be assessed according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) *and immune-related Response (irRC)* criteria (see Appendix 5 *and* Appendix 6).

Patients should be kept in the study until no longer experiencing clinical benefit as determined by the investigator and an effort should be made not to discontinue therapy solely on the basis of an increase in PSA in the absence of other indicators of disease progression.

1 Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. J Clin Oncol 2008;26:1148–59.

Appendix 8
Revised Assessment in Neuro-Oncology Criteria for Patients with Glioblastoma

The response criteria to be used for patients with glioblastoma multiforme (GBM) are based on the Revised Assessment in Neuro-Oncology (RANO) Response Evaluation Criteria. Index and non-index lesions should represent/include all glioblastoma lesions for which disease is present at baseline. Magnetic resonance imaging (MRI) is the most readily available and reproducible method of disease assessment and is required for this study.

The following sequences of the entire brain should be acquisitioned using, at minimum, a 1.5T scanner at each timepoint, with slice thicknesses $\leq$ 5 mm with no gap:

- Axial T1 pre-contrast
- Axial T2 fast spin echo
- Axial fluid-attenuated inversion recovery (FLAIR)
- Axial T1 post-gadolinium (Gd)
- Coronal T1 post-Gd
- Additional imaging may be helpful

  Diffusion (diffusion-weighted imaging [DWI], apparent diffusion coefficient [ADC])

I. DEFINITIONS

A. Measurable Lesions

1. Measurable lesions are lesions with clear borders that can be accurately measured in two dimensions with one diameter $\geq$ 1.0 cm (10 mm) at baseline.
2. Measurements must be performed on the outer diameters of the contrast-enhancing lesions identified on the post-Gd contrast-enhanced MRI. Lesions with cystic components will have the cystic components included in the measurements. Lesions that do not enhance will be considered non-index lesions and must not be measured. Surrounding white matter edema and mass effect will not be considered measurable. Do not include cavity, cyst, or necrosis in the measurement.
3. Index and non-index lesions should represent/include all intra-axial and extra-axial CNS lesions for which disease is present at baseline. In some cases, non-index lesions may be measurable (e.g., if the number of measurable lesions exceeds the maximum number of target lesions [10] to be followed). In this case, “additional” measurable lesions should be followed as non-index lesions, and measurements should not be recorded.

See Table 1 for an overview of types of lesions.

Appendix 8
Revised Assessment in Neuro-Oncology Criteria for Patients with Glioblastoma (cont.)

Table 1 Lesion Categories

Type of Lesion	Index Lesion	Non-Index Lesion
Measurable	Yes	Possible
Non-measurable	No	Yes

B. Index Lesions

1. Index lesions must be measurable (as described above; see Table 1) and can include all measurable lesions up to a maximum of five. Any additional measurable lesions above this maximum number should be followed as non-index lesions.
2. Index lesions should be selected on the basis of their size (lesions with the longest diameter or cross product) and their suitability for accurate repetitive measurements by MRI.
3. Index lesions can only include lesions that show enhancement on MRI after administration of intravenous (IV) contrast.

C. Non-Index Lesions

1. Non-index lesions are defined as lesions that are evident on radiographic examination that cannot be accurately measured by ruler or calipers, do not meet criteria for measurable lesions (see Section A), or exceed the allowable number of index lesions.
2. Examples of non-index lesions include:

- Lesions that do not enhance with IV contrast (i.e., seen only on T2/FLAIR)
- Lesions with both diameters < 10 mm
- Lesions with unclear borders
- Leptomeningeal disease
- Groups of lesions that are small (< 1.0 or < 2.0 cm, depending on imaging method used) and numerous

II. TUMOR ASSESSMENT

A. Methods of Tumor Assessment

1. MRI scans must be used for the selection and measurements of index lesions.
2. The same lesions selected at baseline must be assessed at each subsequent timepoint.
3. Sequences, contrast administration, slice thickness, and plane of acquisition must be kept consistent across visits. Other parameters should be as close to the baseline examination as possible, allowing for slight differences in vendor imaging equipment.
4. Additional imaging other than MRI may be needed to assess acute neurologic changes. Such examinations cannot be used to assess response and cannot replace the required MRI

scans outlined in the protocol (i.e., a patient is being followed by MRI and develops symptoms of acute intracranial hemorrhage; in this instance, non-contrast CT might be performed to exclude intracranial hemorrhage).

III. PERFORMING TUMOR MEASUREMENTS

A. General Guidelines

1. Measurements based on MRI should be taken using calipers and a reference measurement grid. Care should be taken to detect any changes in the relative magnification of the images.
2. The size of index lesions will be recorded in millimeters.
3. The bi-perpendicular diameters of three-dimensional lesions should be assessed in the same plane that the image was acquired. However, when possible, the lesions should be measured in the axial plane as images are universally acquired in the axial plan and will allow serial measurements. All subsequent measurements should be made in the same plane that the measurements were made at baseline. Specifically, if measurements were made on lesions in the axial plane at baseline, all subsequent measurements should also be made in the axial plane.
4. The bi-perpendicular measurements of the lesions will be multiplied to determine the area of each index lesion.
5. The area of the index lesions will be summed to determine the sum of the products of the diameters (SPD) of the index lesions. The baseline SPD will be used to assess the response of the index lesions at each timepoint. The SPD of the nadir will be used to judge progression.

B. Reporting Measurements of Index Lesions

1. The longest diameter of the two dimensions should be reported first (e.g., for a lesion that is 20 mm $\times$ 15 mm, "20 $\times$ 15" should be reported.
2. Index lesions that have disappeared completely should be reported as "0 $\times$ 0" mm.
3. When index lesions shrink but are still present but with any diameter $<$ 5 mm, the default value of 5 mm should be reported to the diameter at that assessment. For the purposes of calculating the SPD, 5 mm should be used for the default entry for each dimension of a lesion that is less than 5 mm.
4. Index lesions that cannot be reliably measured for any other reason (e.g., radiograph is not comparable to baseline or is of poor quality) should be reported as "unable to evaluate" (UE).

C. Assessment of Non-Index Lesions

1. Quantitative measurements of non-index lesions will not be reported. However, qualitative assessment of each non-index lesion will be made at each timepoint.

2. Individual non-index lesions will be reported at each timepoint as being “present,” “absent,” or “UE” (meeting the definition for UE as defined above).

IV. DETERMINING RESPONSE

A. Objective Response of Index Lesions

Complete Response (CR): The disappearance of all index lesions by two observations not fewer than 4 weeks apart, with no evidence of progressive disease. A confirmation scan must be acquired at least 4 weeks after the observed response for a classification of CR.

Partial Response (PR): A 50% or more decrease in the SPD and the greatest perpendicular diameter of all index lesions compared to baseline by two observations not less than 4 weeks apart, with no evidence of progressive disease.

Stable Disease (SD)/No Change: Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease. SD does not require confirmation.

Progressive Disease (PD): An increase of 25% or more in the SPD and the greatest perpendicular diameter of index lesions compared with the smallest recorded sum (nadir) during the study or appearance of one or more new lesions.

B. Objective Response of Non-Index Lesions

CR: The disappearance of all non-index lesions by two observations not fewer than 4 weeks apart, with no evidence of progressive disease.

PR: Not applicable for the non-index lesions.

SD/No Change: No significant change in non-index lesions to qualify for either complete response or progressive disease.

PD: Appearance of one or more new lesions that represent unequivocal progression of existing non-index lesions. In the instance where the determination of PD is based only on progression of non-index lesions, the definition of unequivocal progression of non-index lesions will be that the lesion has doubled compared with nadir and must measure greater than 10 mm in one dimension. If these criteria are not met, the patient will not have progressed.

C. Overall Radiographic Response

CR: Complete response of both index and non-index lesions.

PR: Either a complete response of index lesion(s) with no change of non-index lesion(s) or a partial response of index lesion(s) with no progression of non-index lesion(s).

SD: Stable disease of index lesion(s) with no progression of non-index lesion(s).

PD: Progression of either index or non-index lesions.

An integrated MRI response assessment table is provided below.

Table 2 Integrated MRI Response Assessment

Index Lesions	Non-Index Lesions	New Lesions	Overall MRI Response at This Timepoint
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	UE
PR	CR/SD	No	PR
PR	UE	No	UE
SD	CR/SD	No	SD
SD UE No UE	UE	No	UE
PD	ANY	Yes/No	No PD
ANY	PD	Yes/No	PD
ANY	ANY	Yes	PD
UE	Non-PD	No	UE

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; UE = unable to evaluate.

D. Overall Response Determination

In order to make a final response determination, consideration of corticosteroid dose must be included.

CR: In addition to a determination of complete response based on MRI, the patient must not be taking corticosteroids above physiologic levels (i.e., equivalent of 20 mg of hydrocortisone per day).

PR: In addition to meeting MRI criteria for partial response, the corticosteroid dose at the time of the MRI must be no greater than the maximum dose used in the first 6 weeks from initiation of therapy.

SD/No Change: Meets MRI criteria for stable disease; corticosteroid does not change determination of stable disease.

Appendix 8
Revised Assessment in Neuro-Oncology Criteria for Patients with Glioblastoma (cont.)

PD: Meets MRI criteria for progressive disease; corticosteroid dose does not change determination of progressive disease.

Patients who are discontinued from study based on a clinical determination of disease progression in the absence of an MRI scan that documents progression (i.e., either the MRI was not performed or was performed and the tumor measurements did not meet one of the criteria for progression in table above) will be considered to have progressed on the date that the clinical progression was determined. Although clinical progression is not specifically defined in the modified World Health Organization (WHO) criteria, it will be incorporated in this study based on the determination of the investigator that the patient is considered to have clearly worsened neurologically. Further definition of clear worsening is difficult to describe because progression in the brain can present in numerous ways.

Guideline for determining pseudoprogression:

- Enhancement that simulates tumor growth, most often caused by radiation (whole brain or focal)
- Growth of existing lesions or appearance of new lesions within 12 weeks of completion of radiation therapy may be the result of treatment effects rather than growth of tumor.
- Continued follow-up imaging can determine whether initial lesion growth was true progression or pseudoprogression.

  If lesion continues to enlarge, the initial growth is called true progression.

  If lesion stabilizes or shrinks, the initial growth is confirmed as pseudoprogression.

  In such cases, the baseline SPD is no longer included when choosing the nadir value for the purposes of determining when progression occurs.
- Diffusion weighted imaging can help distinguish pseudoprogression from true tumor growth, but its use is still experimental. The use of MR perfusion and spectroscopy is also being explored.

Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963–72.

Appendix 9
Tumor-Type Specific Inclusion and Exclusion Criteria

PROSTATE CANCER

Inclusion criteria:

- Received at least one of the following prior regimens for metastatic castration-resistant prostate cancer: Sipuleucel-T or enzalutamide

  Patients who received prior systemic immunostimulatory agents (including but not limited to anti–CTLA-4, vaccine other than Sipuleucel-T) may be eligible after consultation with Medical Monitor.

- Ongoing androgen deprivation, with serum testosterone < 50 ng/dL

GLIOBLASTOMA MULTIFORME

Inclusion criteria:

- Histologically confirmed glioblastoma multiforme (GBM) in first or second relapse

  A pathology report constitutes adequate documentation of histology for study inclusion. Patients with an initial diagnosis of a lower grade glioma are eligible if a subsequent biopsy is determined to be GBM.

- An interval of ≥ 4 weeks since prior surgical resection
- Received prior standard radiation and/or temozolomide as prior chemotherapy

  An interval of ≥ 8 weeks since prior radiotherapy to minimize the potential for magnetic resonance imaging (MRI) changes related to radiation necrosis that might be misdiagnosed as progression of disease, or ≥ 4 weeks if a new lesion develops—relative to the pre-radiation MRI— that is outside the primary radiation field.

- Prior therapy with gamma knife or other focal high-dose radiation is allowed but the patient must have subsequent histologic documentation of recurrence, unless the recurrence is a new lesion outside the irradiated field

Exclusion criteria:

- Need for urgent palliative intervention for primary disease (e.g., impending herniation)
- Ongoing requirement for dexamethasone

  Patients on dexamethasone ≤ 4 mg/day may be enrolled after consultation with the Medical Monitor

  Patients *receiving* a stable dose of anticonvulsants are permitted.

- Evidence of recent hemorrhage on baseline MRI of the brain with the following exceptions:

  Presence of hemosiderin

  Resolving hemorrhagic changes related to surgery

  Presence of punctate hemorrhage in the tumor

Appendix 9
Tumor-Type Specific Inclusion and Exclusion Criteria (cont.)

HEPATOCELLULAR CARCINOMA

Inclusion criteria:

- The patient has disease that is not amenable to a curative treatment approach (i.e., resection, transplantation)
- Willing to undergo *newly collected* liver biopsy
- Child-Pugh Score of A
- Albumin ≥ 3 g/dL
- Documented virology status of hepatitis, as confirmed by screening hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), and/or anti–hepatitis C virus (HCV)
- Antiviral therapy per local standard of care if active hepatitis B virus (HBV) or HCV infection

    For patients with HBV infection:

        HBV DNA ≤ 500 IU/mL for at least the preceding 3 months

        Willing to take anti-HBV treatment (e.g., entecavir) for the length of the study

        Ongoing anti-HBV treatment (e.g., entecavir) at study entry and for a minimum of 3 months prior to study entry

    For patients with HCV infection:

        Prior and/or ongoing anti-HCV treatment is recommended

Exclusion criteria:

- Concomitant anticoagulation, at therapeutic doses, with anticoagulants
- Patients with untreated or incompletely treated varices with bleeding or high-risk for bleeding
- Moderate or severe ascites
- Co-infection of HBV and HCV

Appendix 10
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 11
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 12
Modified Response and Progression Criteria—Lymphoma

SELECTION OF TARGET LESIONS

Up to six of the largest dominant nodes or tumor masses should be selected according to all of the following (ideally a minimum of three lesions should be chosen):

- Clearly measurable in at least two perpendicular dimensions
- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent timepoint. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions. Examples of non-target lesions include:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly
- Irradiated lesions
- Measurable lesions beyond the maximum number of six chosen as target lesions
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites
- 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.

    Existing effusions/ascites: effusions, ascites, or other fluid collections will be followed as non-target lesions. At each timepoint, 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 that are radiographically suggestive of malignancy should be recorded as new lesions.

Appendix 12
Modified Response and Progression Criteria—Lymphoma (cont.)

REPORTING CONVENTIONS

UNABLE TO EVALUATE (UE) LESION CATEGORY

This category is reserved for target and non-target lesions that are deemed unevaluable because subsequent (post-baseline) examinations had not been performed, lesions could not be evaluated due to poor radiographic technique or poorly defined margins, or lesions identified at baseline were not at a subsequent timepoint.

Examples of UE lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe, or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples, the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller. Another example is the instance when lesions identified at baseline were not imaged at a subsequent timepoint. Lesions that cannot be measured or evaluated will be classified for that timepoint as UE.

If a target lesion is classified as UE post-baseline, the sum of the products of the diameters (SPD)/area (whichever applies) of the target lesions cannot accurately be determined for that timepoint, a response of complete response (CR), partial response (PR), or stable disease (SD) cannot be assigned for that timepoint and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions or the evaluable target lesions.

Progressive disease (PD) can be determined without evaluation of all sites of disease based on the greatest tumor dimension (GTD), area, or SPD for target lesions, evaluation of unequivocal progression in non-target lesions, or observation of a new lesion within the available radiographic or clinical assessments.

TOO SMALL TO MEASURE (TSTM) LESION CATEGORY

Any target lesion findings identified on baseline images, which at a subsequent timepoint decreases in size to < 5 mm in any dimension, should be categorized as TSTM. The lesion, node, or mass should be assigned measurements of 5 mm $\times$ 5 mm (for the GTD and the short axis) on the source document for the purpose of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterwards, its true size (GTD and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

Appendix 12
Modified Response and Progression Criteria—Lymphoma (cont.)

Table 1 Timepoint Response

Target Lesions	Non-Target Lesions	New Lesions [a]	Timepoint Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	UE
PR	UE	No	UE
PR	CR	No	PR
PR	SD	No	PR
SD	UE	No	UE
SD	CR	No	SD
SD	SD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
UE	Non-PD	No	UE
UE	UE	No	UE
CR	NA [c]	No	CR
PR	NA [c]	No	PR
SD	NA [c]	No	SD
NA [b]	SD	No	SD
NA [b]	CR	No	CR
NA [b]	UE	No	UE
NA [b]	NA [c]	No	UE

CR = complete response; NA= not applicable; PD = progressive disease; PR = partial response; SD = stable disease; UE = unable to evaluate.

Note: Modified from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

[a] Identification of new lesions at a post-baseline timepoint will result in a response assessment of PD. If an identified new lesion subsequently becomes UE, the timepoint response will be recorded as PD unless the new lesion has proven to have resolved.

[b] No target lesions identified at baseline.

[c] No non-target lesions identified at baseline.

Appendix 12
Modified Response and Progression Criteria—Lymphoma (cont.)

COMPLETE REMISSION

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy
2. A) Typically ^{18}fludeoxyglucose (FDG)-avid lymphoma: In patients with no pre-treatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

   B) Variably FDG-avid lymphomas/FDG avidity unknown: In patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size ($\leq$ 1.5 cm in their greatest transverse diameter for nodes $>$ 1.5 cm before therapy). Previously involved nodes that were 1.1–1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to $<$ 1.0 cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
4. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate ($>$ 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a complete remission until data become available demonstrating a clear difference in patient outcome.

PARTIAL REMISSION

1. $\geq$ 50% decrease in SPD of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following:

   They should be clearly measurable in at least two perpendicular dimensions

   If possible, they should be from disparate regions of the body

   They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exceptions of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a partial remission if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders.
6. No new sites of disease should be observed (e.g., nodes >1.5 cm in any axis).
7. Typically FDG-avid lymphoma: For patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

STABLE DISEASE

1. Failing to attain the criteria needed for complete remission or partial remission but not fulfilling those for progressive disease (see below)
2. Typically FGD-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Appendix 12
Modified Response and Progression Criteria—Lymphoma (cont.)

RELAPSED DISEASE (AFTER COMPLETE REMISSION) OR PROGRESSIVE DISEASE (FOR PATIENTS WITH PARTIAL REMISSION OR STABLE DISEASE)

Lymph nodes should be considered abnormal if the long axis is >1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm, it should be considered abnormal only if its short axis is >1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size; increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Adapted from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

Appendix 13
Response Criteria—Multiple Myeloma

For the purposes of this study, stringent complete response will be assessed as complete response. Very good partial response will be assessed as partial response. Minimal response will be equivalent to stable disease.

Response Subcategory	Response Criteria [a]
sCR	CR as defined below plus: • Normal FLC ratio and absence of clonal cells in bone marrow [b] by immunohistochemistry or immunofluorescence [c]
CR	• Negative immunofixation on the serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • ≤5% plasma cells in bone marrow [b] • If during study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio
VGPR	PR as defined below plus all of the following: • Serum and urine M-protein detectable by immunofixation but not on electrophoreses, or • 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours • If during study, the only measurable non-bone marrow parameter was FLC, 90% or greater reduction in the difference between involved and uninvolved FLC levels
PR	≥50% reduction of serum M-protein and • Reduction in 24-hour urinary M-protein by ≥90% or to <200 mg per 24 hours • If during study, only serum measurable (but urine not), a 50% or greater reduction of serum M-protein • If during study, urine measurable (but serum not), a reduction in 24-hour urinary M-protein by 90% or greater or to <200 mg per 24 hours • If during study, the only measurable non-bone marrow parameter was FLC, a 50% or greater decrease in the difference between involved and uninvolved FLC levels • If during study, the bone marrow was the only measurable parameter, a 50% or greater reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was at least 30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
MR	• At least 25% but <49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50%–89%, which still exceeds 200 mg per 24 hours In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in the size of soft tissue plasmacytomas is also required.
SD	Not meeting criteria for sCR, CR, VGPR, PR, MR, or PD

Appendix 13
Response Criteria—Multiple Myeloma (cont.)

Response Subcategory	Response Criteria [a]
PD [d]	Increase of ≥25% from baseline or nadir in (any one or more of the following): • Serum M-protein (increase must be ≥0.5 g/dL) [e], and/or • Urine M-protein (increase must be ≥200 mg per 24 hours), and/or • Marrow plasma cell percentage (absolute % must be ≥10% [f]) • If during study, the only measurable non-bone marrow parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) Or any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder: • New or increased in size of existing plasmacytomas or bone lesions • Hypercalcemia due to myeloma (>11.5 mg/dL or 2.65 mmol) • Decrease in hemoglobin of at least 2 g/dL • Serum creatinine level at least 2 mg/dL
Relapse from CR or sCR [g]	Patient who has achieved confirmed CR who has any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of at least 5% plasma cells in the bone marrow [h] • Appearance of any other sign of progression

CR=complete response; EBMT=European Group for Blood and Marrow Transplantation; FLC=free light chain; IMWG=International Myeloma Working Group; M-protein=monoclonal immunoglobulin protein; MR=minimal response; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

[a] All response categories require two consecutive assessments made at any time before the institution of any new therapy (at least 4 weeks apart); CR, PR, MR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. The above categories and criteria are derived from both the EBMT and IMWG Uniform Response Criteria.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is of >4:1 or <1:2.

[d] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of new therapy.

[e] For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[f] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[g] Positive immunofixation alone in a patient previously classified as CR will not be considered progression.

[h] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

Appendix 13
Response Criteria—Multiple Myeloma (cont.)

Adapted from:

Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and hemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102:1115–23.

Durie BG, Harousseau JL, Miguel JS, et al. International Uniform Response Criteria for multiple myeloma. Leukemia 2006;20:1467–73.

INTERIM STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB ADMINISTERED INTRAVENOUSLY AS A SINGLE AGENT TO PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES**
PROTOCOL NUMBER:	PCD4989g
STUDY DRUG:	Atezolizumab (MPDL3280A)
IND NUMBER:	111271
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	Redacted
DATE FINAL:	See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

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1. BACKGROUND

Atezolizumab (MPDL3280A) is a humanized 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 programmed death−ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death−1 (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 for solid tumors and hematologic malignancies in humans.

This document specifies the statistical analyses for Study PCD4989g. Analyses outlined in this interim Statistical Analysis Plan (iSAP) will supersede those specified in Protocol PCD4989g for the purposes of a regulatory filing.

2. STUDY DESIGN

This Phase I, multicenter, first-in-human, open-label, dose-escalation study evaluates the safety, tolerability, and pharmacokinetics of atezolizumab administered as a single agent by intravenous (IV) infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies. Figure 1 illustrates the study design.

Approximately eight dose levels ranging from 0.01 to 20 mg/kg (the proposed doses were 0.01, 0.03, and 0.1 mg/kg as single-patient cohorts and 0.3, 1, 3, 10, and 20 mg/kg as 3+3 cohorts) were evaluated to determine the maximum tolerated dose (MTD) or the maximum administered dose (MAD) of atezolizumab in the dose-escalation stage of the study. Depending on new nonclinical efficacy, clinical safety, and clinical pharmacokinetic (PK) data, additional intermediate dose levels and/or different schedules (with dosing no more frequently than once a week) might have been evaluated during the dose-escalation stage after consultation with the study investigators.

Prior to the determination of the MTD or MAD, additional patients might have been enrolled and treated in expansion cohorts at doses of ≤10 mg/kg to better characterize the safety, tolerability, PK variability, and preliminary efficacy of single-agent atezolizumab. Up to approximately 10 patients with renal cell carcinoma (RCC), 10 patients with melanoma, and 10 patients with non−small cell lung cancer (NSCLC)

were planned to be enrolled in each expansion cohort after the 10-mg/kg dose level was determined to be safe in a minimum of 3 patients.

After the determination of the MTD or MAD, additional patients were enrolled and treated in expansion cohorts at doses and schedules selected to result in a total drug exposure less than or equal to exposures achieved at the MTD or MAD. Expansion cohorts to be used were 10, 15, and 20 mg/kg of atezolizumab. In order to further characterize the safety of atezolizumab and to assess biomarkers of tumor activity in different cancer types, the expansion cohorts included approximately

- 40 patients with RCC
- 40 patients with NSCLC
- 20 patients with melanoma
- Approximately 590 patients with solid tumors or hematologic malignancies were planned to be enrolled. After discussion with the study investigators, prospective enrollment of patients were based on potential predictive tumor characteristics (e.g., PD-L1–positive status; in the United States, this applied only in Investigational Device Information [IDI] indications after IDI submission to the Center for Devices and Radiological Health [CDRH]). Twenty patients with tumors that were amenable to serial biopsy were also enrolled at the selected dose and schedule. Serial tumor biopsies were performed for those 20 patients but are optional for all other patients.

This study is conducted at approximately 20 sites both inside and outside the United States. The sample size for this trial was determined by the dose-escalation rules described in Section 3.1.1 of Protocol PCD4989g, as well as by the number and size of the expansion cohorts. Approximately 656 to 689 patients will be enrolled in this trial.

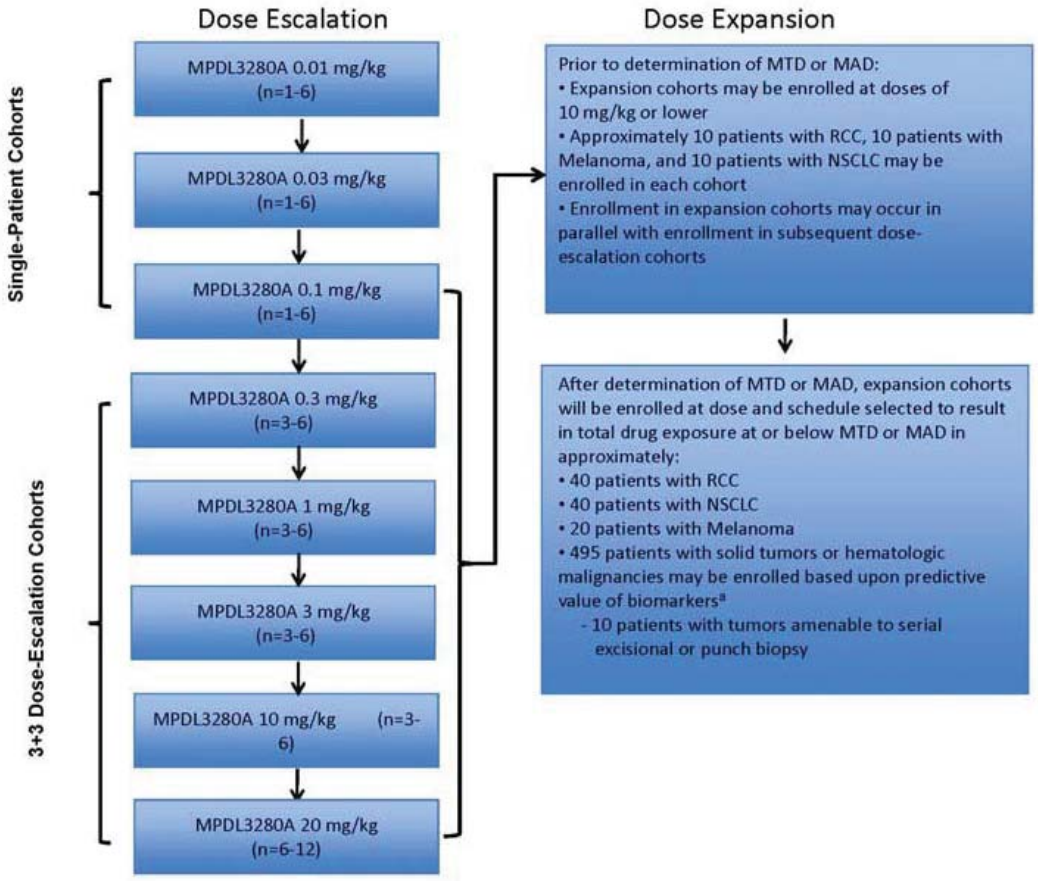
Tumor assessment by scan is scheduled every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until the patient dies, experiences disease progression, or initiates further systemic cancer therapy or the study closes, whichever occurs first.

All patients return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. All adverse events are recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Ongoing adverse events thought to be related to study treatment are followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer 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 adverse event.

The protocol was amended so that all patients are followed for survival post-treatment discontinuation and during follow-up periods until withdrawal of consent, loss of follow-up, death, or until study termination by the Sponsor, whichever occurs first.

Figure 1 Study Design: Proposed Cohorts



IDI = investigational device information; MAD = maximum administered dose; MTD = maximum tolerated dose; NSCLC = non−small cell lung cancer; PD-L1 = programmed death−ligand 1; RCC = renal cell carcinoma.

[a] Prospective enrollment based on potential predictive tumor characteristics (e.g., PD-L1 + status; in the United States, only in IDI indications once IDI submitted to the Center for Devices and Radiological Health) was implemented. See Section 3.1.2 of Protocol PCD4989g for more details.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. For additional details, see the study flowcharts in Appendix 2 and Appendix 3.

2.2 OUTCOME MEASURES

2.2.1 Safety Outcome Measures

The safety and tolerability of atezolizumab administered as a single-agent therapy for patients with locally advanced or metastatic solid tumors or hematologic malignancies will be assessed using the following primary safety outcome measures:

- Incidence and nature of dose-limiting toxicities (DLTs)
- Incidence, nature, and severity of adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 (NCI CTCAE v4.0)

Additionally, safety will be assessed using the following secondary safety endpoints:

- Incidence of anti-therapeutic antibody (ATA) response and the potential correlation with PK, pharmacodynamic, and safety parameters
- Changes in vital signs and ECG parameters
- Changes in clinical laboratory results
- Number of cycles and dose intensity

2.2.2 Pharmacokinetic Outcome Measures

The following PK data will be derived from the concentration-time data of atezolizumab when appropriate and when applicable:

- Area under the concentration-time curve (AUC)
- Maximum serum concentration (C_{max})
- Minimum serum concentration (C_{min})
- Clearance (CL)
- Volume at steady state (V_{ss})

Other parameters, such as accumulation ratio, half-life, and dose proportionality, may also be calculated.

2.2.3 Efficacy Activity Outcome Measures

The activity outcome measures are as follows:

- Best overall response (BOR) rate in patients with solid malignancies per investigator assessment based on RECIST v1.1
- Objective response rate (ORR) per investigator assessment based on RECIST v1.1
- Duration of response (DOR) per investigator assessment based on RECIST v1.1
- 24-week progression-free survival (PFS)
- 1-year overall survival (OS)

- The efficacy analysis (ORR and DOR) in patients with urothetial bladder cancer (UBC) will also use the clinical response assessed by an independent review facility (IRF) per RECIST v1.1

2.2.4 Exploratory Outcome Measures

The following exploratory activity outcome measures will be assessed:

- PFS per investigator assessment based on RECIST v1.1
- OS
- Time in response (TIR) per investigator assessment based on RECIST v1.1
- PFS in responders per investigator assessment based on RECIST v1.1
- Time to onset of response (TTOR) per investigator assessment based on RECIST v1.1
- ORR by immune-modified RECIST

The following exploratory biomarker endpoints will be assessed when appropriate.

- Status of PD-L1 and other exploratory biomarkers in tumor tissue
- Changes in T, B, and natural killer (TBNK) numbers (TBNK assay) in blood
- Changes in various T-cell subpopulations in blood (e.g., effector/memory T cells, regulatory T cells, and other T-cell types)

  Identification and profiling of exploratory biomarkers in peripheral blood mononuclear cells (PBMCs) (e.g., changes in expression of CD25 or human leukocyte antigen DR [HLA-DR], interferon [IFN]-γ production, and other markers)
- Changes in tumor-infiltrating, CD8+ T cells with PD-L1 staining, and other immune cells/exploratory markers in atezolizumab pre-treatment, on-treatment, and post-treatment tumor tissue

  Identification and profiling of exploratory biomarkers in plasma (i.e., interleukin [IL]-2, IFN-γ, and other markers)

  Changes in tumor-infiltrating T-cell activity (measured by expression of granzyme B and other markers) in atezolizumab pre-treatment, on-treatment, and post-treatment tumor tissue
- Enumeration of circulating tumor cell (CTCs) in blood

Results on these exploratory biomarker endpoints will not be included in the Clinical Study Report (CSR) except for analyses listed below.

2.3 DETERMINATION OF SAMPLE SIZE

The dose-escalation stage sample size for this trial is based on the dose-escalation rules described in Section 3.1.1 of Protocol PCD4989g.

Design considerations were not made with regard to explicit power and type I error considerations but were made to obtain preliminary safety, PK, pharmacodynamics, and biomarker information in this patient population. The planned enrollment for this study is approximately 656–689 patients. The study enrolled approximately 21–54 patients in the dose-escalation stage and plans to enroll approximately up to 635 patients in the dose-expansion stage. Within each indication (e.g., RCC, melanoma, NSCLC) of the expansion cohort, the following rule applied: if no responders (complete response [CR] or partial response [PR]) were observed from the first 14 patients who were considered to be more likely to respond on the basis of the presence of biomarkers potentially predictive of anti-tumor activity, enrollment would be suspended for that indication. With the assumption of a true response rate of 20% or higher, there was at most a 4.4% chance of not observing any response in 14 patients.

With an observed response rate of 30%, a sample size of 40 patients within a given indication (i.e., RCC, NSCLC) would result in a 90% confidence CI of 19.96%–42.87%. The corresponding 90% CI with 20 patients would be 16.39%–48.38%.

Any patient who did not complete the DLT assessment window for any reason other than a DLT was considered non-evaluable for dose-escalation decisions and MTD assessment and was replaced by an additional patient at that same dose level.

Table 1 describes the probability of not observing any DLTs in 1 patient, the probability of not observing any DLTs in 3 patients, and the probability of observing fewer than two DLTs in 6 patients for different underlying DLT rates during the dose-escalation stage.

Table 1 Probability of Observing DLTs for Different Underlying DLT Rates

Underlying DLT Rate	Probability of Observing No DLTs in 3 Patients	Probability of Observing Fewer Than Two DLTs in 6 Patients
0.10	0.73	0.89
0.20	0.51	0.66
0.33	0.30	0.36
0.40	0.22	0.23
0.50	0.13	0.11
0.60	0.06	0.04

DLT = dose-limiting toxicity.

To better characterize the safety of the single-agent MTD identified in the dose-escalation stage, additional expansion cohorts of approximately 40 patients (in RCC and NSCLC) were planned to be enrolled. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such adverse event in a

given cohort of 6 patients was 47%, 26%, and 5.8%, respectively. The corresponding probabilities of observing at least one such adverse event in an expanded cohort of 40 patients increased to 98.5%, 87.1%, and 33.1%, respectively.

Note: In light of emerging data, enrollment of patients into the RCC, NSCLC, and melanoma expansion cohorts, as well as the enrollment of UBC patients, expanded beyond the planned sample size in order to further understand the safety, tolerability, efficacy, pharmacokinetics, and biomarkers in these patients and in the PD-L1–diagnostic patient subgroups. As of 2 September 2014, a total of 444 patients enrolled in the study across multiple tumor types including bladder (n = 95), non–small cell lung (n = 88), renal (n = 69), melanoma (n = 45), breast (n = 27), head and neck (n = 29), colorectal, gastric (n = 14), ovarian (n = 12), and other tumor types. Patients with prostate cancer, hepatocellular cancer, and patients with glioblastoma multiforme will not be included in the CSR as they were enrolled after clinical data cutoff (i.e., 2 December 2014).

3. OVERALL ANALYSIS PLAN FOR STUDY PCD4989g

3.1 STATISTICAL METHODS

Analyses will be based on patient data collected up to the clinical cutoff date of 2 December 2014.

Safety and efficacy results will be summarized overall for each of the tumor types with more than 10 patients enrolled by the clinical cutoff date.

PD-L1 diagnostic status will be used in efficacy analysis for UBC and NSCLC patients. There are 4 PD-L1 scores in tumor-infiltrating immune cell (IC; IC0, IC1, IC2, and IC3) and in tumor cell (TC; TC0, TC1, TC2, and TC3). The PD-L1 score of IC2/3 corresponds to IC2 and IC3 grouped.

Safety results will be summarized overall across all tumor types and by dosing cohorts.

3.1.1 Analysis Populations

3.1.1.1 Safety-Evaluable Population

The safety-evaluable population is defined as all enrolled patients of all tumor types who received any amount of atezolizumab on study.

3.1.1.2 Efficacy-Evaluable Population

The efficacy-evaluable population is defined as safety-evaluable patients who received ≥ 1-mg/kg dose of atezolizumab in Phase I formulation or any amount of atezolizumab in Phase III formulation. This analysis population will be used for all efficacy analyses except for ORR, DOR, BOR, TTOR, and TIR (see Section 3.1.1.3).

3.1.1.3 Objective Response–Evaluable Population

The objective response–evaluable population is defined as the efficacy-evaluable population with measurable disease per RECIST v1.1 at baseline. This analysis population will be used for all efficacy analyses of ORR, BOR, and TIR.

DOR and TTOR analyses will be performed on the subset of patients who achieve an objective response.

Except for certain tumor types (see below for indication-specific sections), a no-minimum follow-up duration is used to define the objective response–evaluable population used to summarize ORR, DOR, TTOR, and TIR results.

3.1.1.4 Pharmacokinetic-Evaluable Population

The PK-evaluable population is defined as treated patients with PK data at timepoints that are sufficient to determine PK parameters

3.1.2 Analysis of Study Conduct

Enrollment criteria exceptions, major protocol violations, study treatment administration, and reasons for patient discontinuations from the study will be described and summarized.

3.1.3 Safety Analyses

Safety results will be summarized overall across all tumor types and by dosing cohorts, based on the safety-evaluable population. Safety will be assessed through summaries of DLTs, adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to atezolizumab. QTc-exposure analyses will be reported in a separately.

Safety summaries for treatment-emergent adverse events will include all adverse events that occur on or after the first dose of study drug until the earliest of the following:

- 30 days after the last administration of study drug
- Initiation of another non-protocol anti-cancer therapy after the last administration of study drug
- Clinical cutoff date

Summaries of serious adverse events related to treatment, adverse events of special interest (AESIs), and all safety listings will include adverse events with an onset date on or after the date of the first dose of study drug up to the data cutoff date. The AESIs will be derived from Sponsor-defined adverse event group terms consisting of preferred terms representing immune-mediated reactions.

Multiple occurrences of the same event will be counted once at the maximum severity.

3.1.3.1 Exposure of Study Drug

Study drug exposure, including treatment duration and number of cycles, will be summarized for each dose cohort with descriptive statistics for the study overall (including all tumor types) and separately for each tumor type with more than 10 patients.

3.1.3.2 Adverse Events

Verbatim descriptions of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the NCI CTCAE v4.0. Adverse event data will be listed by study site, dose cohort, patient number, and study day. Multiple occurrences of the same event will be counted once at the maximum severity for each patient.

In addition, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to the declaration of DLTs will be listed and summarized separately. Patients who withdraw from the study prior to completing the DLT assessment window (Day 21) for reasons other than a DLT will be considered unevaluable for DLT and MTD assessments.

Deaths reported within and beyond 30 days after last study dose will be summarized by dose cohort. Causes of deaths will be summarized by dose cohort.

3.1.3.3 Laboratory Data and Vital Signs

Relevant laboratory collected within 30 days of the last administration of study drug and vital signs data will be displayed by time, with NCI CTCAE v4 Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data collected within 30 days of the last administration of study drug will be summarized by grade with use of NCI CTCAE v4.0.

3.1.3.4 Anti-Therapeutic Antibody

Incidence of ATA response and the potential correlation with PK, pharmacodynamic, and safety parameters will be assessed.

3.1.4 Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum atezolizumab concentration versus time data will be tabulated and plotted by dose level. The pharmacokinetics of atezolizumab will be summarized by estimating total AUC, C_{max}, C_{min}, total CL, V_{ss}, and terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, and coefficient of variation). Interpatient variability and drug accumulation will be evaluated.

Additional PK and PD analyses will be conducted as appropriate.

3.1.5 Efficacy (Activity) Analyses

Efficacy results will be summarized separately for each tumor type with more than 10 patients enrolled by the clinical cutoff date. Efficacy will not be summarized overall for all patients across tumor types. BOR rate, ORR, and DOR analyses will be performed on the objective response–evaluable population for all tumor types. TIR and TTOR will be performed for UBC and NSCLC patients. OS and PFS analyses will be performed on the efficacy-evaluable population. If PD-L1 status is available for UBC and NSCLC patients, then ORR will also be summarized by this status.

BOR rate, ORR, DOR, and PFS analyses described in Sections 3.1.5 and 3.1.6 will be conducted on the basis of responses as assessed by both RECIST v1.1 and immune-related RECIST criteria (irRC) in patients with solid malignancies; assessment using RECIST v1.1 will be considered the primary analyses, and corresponding assessment using irRC to more adequately assess activity of immunotherapeutic agents will be considered a sensitivity analysis.

In patients with malignant lymphoma or multiple myeloma, their respective disease-specific criteria will be used to evaluate objective response and disease progression: 2007 Revised International Working Group (IWG) Criteria in patients with malignant lymphoma and as International Myeloma Working Group (IMWG) Uniform Criteria with consecutive assessment $\geq$4 weeks later in patients with multiple myeloma.

3.1.5.1 Objective Response per RECIST v1.1

Objective response is defined as a CR or PR, as determined by investigator assessment and confirmed by repeat assessment $\geq$4 weeks after initial documentation. Reponses for patients with malignant lymphoma and multiple myeloma will be assessed with a separate use of disease-specific criteria.

ORR will be estimated and 95% CI for the estimated rate will be constructed using the Clopper-Pearson method.

Patients with missing or no response assessments will be classified as non-responders.

3.1.5.2 Duration of Response per RECIST v1.1

Among patients with an objective response, DOR will be defined as the time from the initial complete or partial response to the time of disease progression or death, whichever occurs first.

The median DOR will be estimated by Kaplan-Meier methodology for the individual tumor types, with the 95% CI constructed using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982).

For patients who do not die or experience disease progression by the clinical cutoff date or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment.

3.1.5.3 Best Overall Response per RECIST v1.1

BOR is defined as the best response recorded from the start of the study treatment until the end of treatment. BOR does not need confirmation and can occur at any time following the first atezolizumab dose and prior to any additional systemic anti-cancer therapy.

The BOR rate will be estimated and summarized using the same methodology used for the objective response described in Section 3.1.5.1.

3.1.5.4 6-Month Progression-Free Survival Rate per RECIST v1.1

PFS rate at 6 months from the first dose of atezolizumab will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using Greenwood's formula.

3.1.5.5 1-Year Overall Survival Rate

OS rate at 1 year from the first dose of atezolizumab will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using Greenwood's formula.

3.1.6 Exploratory Analyses

3.1.6.1 Overall Survival

OS is defined as the time from the first day of study treatment with atezolizumab (Cycle 1, Day 1) until documented death of any cause.

For the evaluation of OS, Kaplan-Meier methodology will be used to estimate the median OS. For patients who do not have documented death by the clinical cutoff date, OS will be censored at the last day known to be alive. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS (Brookmeyer and Crowley 1982).

3.1.6.2 Progression-Free Survival per RECIST v1.1

PFS is defined as the time from the first day of study treatment with atezolizumab (Cycle 1, Day 1) until documented disease progression or death, whichever occurs first.

For the evaluation of PFS, Kaplan-Meier methodology will be used to estimate the median PFS. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each tumor type (Brookmeyer and Crowley 1982).

For patients who do not have documented progressive disease or death, PFS will be censored at the day of the last tumor assessment.

3.1.6.3 Time in Response per RECIST v1.1

TIR measures the duration of time both responders and non-responders experience an objective response. TIR, for responders, is defined as the DOR. For non-responders,

TIR is defined as the first treatment date plus 1 day and will be considered as an event. Analysis approaches for TIR will be the same as for DOR. TIR will be performed for the UBC and NSCLC patient cohorts.

3.1.6.4 PFS in Responders per RECIST v1.1

PFS will be assessed in patients with confirmed responses per investigator assessment based on RECIST v1.1 in the objective response–evaluable population. The analysis approach used will be the same as that for the PFS analysis.

3.1.6.5 Time to Onset of Response per RECIST v1.1

TTOR is defined as the duration from the first study dose to the first documented investigator-assessed response (i.e., a CR or PR based on RECIST v1.1). The analysis approach used will be the same as that for the DOR analysis. TTOR will be performed for the UBC and NSCLC patient cohorts.

3.1.6.6 Sensitivity Analysis

BOR rate, ORR, DOR, and PFS assessed by irRC will be estimated and summarized using the same methodology described above for each of these endpoints.

For certain tumor types (see below in indication-specific sections) where a minimum follow-up is specified in the objective response–evaluable population used for the primary efficacy analyses (i.e., ORR per RECIST v1.1), sensitivity analyses on the primary efficacy endpoint will be summarized using a no-minimum follow-up.

3.1.7 Missing Data

For analysis on adverse events, any adverse events with missing onset dates will be considered as treatment-emergent adverse events and included in the safety analyses.

For analysis on objective response, BOR, and DOR, patients with missing or no response assessments will be classified as non-responders.

For analysis on PFS, patients who do not have documented progressive disease or death will be censored at the last tumor assessment on the study. Similarly, for OS, patients who do not have documented death will be censored at the last day known to be alive. For both endpoints, patients with no post-baseline tumor assessments will be censored at the time of first dose plus 1 day.

4. ANALYSIS PLAN SPECIFIC TO UROTHELIAL BLADDER CANCER PATIENTS IN STUDY PCD4989g

This section specifies analyses that are planned for the UBC patients enrolled in Study PCD4989g and will be included in the CSR.

4.1 ANALYSIS POPULATION

4.1.1 UBC Safety-Evaluable Population

The UBC safety-evaluable population is defined as the safety-evaluable population with transitional cell carcinoma (TCC; also called urothelial cell carcinoma) of the urinary tract. The safety-evaluable population is defined in Section 3.1.1.1.

4.1.2 UBC Efficacy-Evaluable Population

The UBC efficacy-evaluable population is defined as the efficacy-evaluable population with TCC of the urinary tract. The efficacy-evaluable population is defined in Section 3.1.1.2.

UBC efficacy-evaluable patients will be summarized by PD-L1 diagnostic status subgroups: IC2/3 based on PD-L1 expression using 1) the PD-L1 IHC investigation use–only (IUO) assay only and 2) the PD-L1 IHC assay at time of enrollment. When a patient has multiple samples tested available within each PD-L1 assay type resulting in multiple PD-L1 scores, the PD-L1 score used for analysis will be the maximum PD-L1 score among the multiple samples.

4.1.3 UBC Objective Response–Evaluable Population

The UBC objective response–evaluable population is defined as the UBC efficacy-evaluable population with measurable disease per RECIST v1.1 at baseline with a minimum of 12 weeks of follow-up.

4.1.4 UBC Pharmacokinetic-Evaluable Population

The UBC PK-evaluable population is defined as the PK-evaluable population with TCC of the urinary tract. The PK-evaluable population is defined in Section 3.1.1.4.

4.2 ANALYSIS OF STUDY CONDUCT

The analysis of study conduct will be same as described for the overall study in Section 3.1.2 but will be performed on the UBC safety-evaluable population.

4.3 SAFETY ANALYSES

The safety analyses will be same as described for the overall study in Section 3.1.3 but will be performed on the UBC safety-evaluable population. Safety results will be summarized for the UBC safety-evaluable population overall and by PD-L1 IHC status, including IC2/3.

4.4 EFFICACY ANALYSES

The efficacy analyses will be same as described for the overall Study PCD4989g in Section 3.1.5 but will be performed and summarized for the UBC efficacy-evaluable population overall and by PD-L1 status, including IC2/3. ORR and DOR will also be assessed in patients with a PD-L1 status of IC0 and IC1. Of note, efficacy results in the overall UBC population may not be reflective of the general UBC population as the

cohort of UBC patients enrolled in Study PCD4989g was enriched in high PD-L1 IC (IC2/3) because of the way in which the cohort was enrolled.

In addition to the endpoints specified in Section 3.1.5, specific to UBC, the following additional efficacy endpoints will also be summarized.

- ORR and DOR as assessed by the IRF per RECIST v1.1
- ORR and DOR as assessed by the investigator per irRC
- 6-month PFS as assessed by the investigator per irRC
- 1-year PFS as assessed by the investigator per RECIST v1.1 and per irRC
- PFS as assessed by investigator per irRC

Rules and guidelines on IRF tumor assessment are outlined separately in an IRF Charter.

4.5 EXPLORATORY ANALYSES

Confirmed ORR as assessed by the IRF and the investigator per RECIST v1.1 will be summarized in the UBC efficacy-evaluable population by subgroups determined by the baseline characteristics including Eastern Cooperative Oncology Group (ECOG) status, smoking status, creatinine clearance, number of prior systemic regimens, liver metastases, visceral metastases (defined as involvement of at least one lesion in bladder, lung, liver, stomach, colon, small bowel, pancreas adrenal gland, bone, or kidney), site of primary tumor (bladder vs. ureter vs. renal pelvis vs. urethra), prior BCG, prior cystectomy or nephroureterectomy, time from last prior chemotherapy to first study drug administration ($\leq$ 3 months vs. $>$3 months), PD-L1 assay type (IUO vs. prototype), tissue type (biopsy, resection, other), by PD-L1 IHC status (IC2/3 vs. IC0/1), by PD-L1 IC scores, by PD-L1 TC scores, and with a no-minimum follow-up period.

5. ANALYSIS PLAN SPECIFIC TO NON–SMALL CELL LUNG CANCER PATIENTS IN STUDY PCD4989g

This section specifies analyses that are planned for the NSCLC patients enrolled in Study PCD4989g and will be included in the CSR.

5.1 ANALYSIS POPULATION

5.1.1 NSCLC Safety-Evaluable Population

The NSCLC safety-evaluable population is defined as all enrolled NSCLC patients who received any amount of atezolizumab on Study PCD4989g.

5.1.2 NSCLC Efficacy-Evaluable Population

The NSCLC efficacy-evaluable population is defined as all enrolled NSCLC patients who received $\geq$1-mg/kg dose of atezolizumab in Phase I formulation or any amount of

atezolizumab in Phase III formulation. This analysis population will be used for all efficacy analyses except for those of ORR, DOR, BOR, TTOR, and TIR.

NSCLC efficacy-evaluable patients could be further classified based on PD-L1 expression (i.e., TC3 or IC3, TC3 or IC2/3, and TC2/3 or IC2/3 population) using the IHC assay: 1) PD-L1 IHC IUO assay (patients without PD-L1 scores using the PD-L1 IHC IUO assay will be using the PDL1 IHC prototype assay) and 2) PD-L1 IHC assay at the time of enrollment as an exploratory approach.

When a patient has multiple samples tested or multiple PD-L1 assay results available, the TC and IC scores of the patient will be determined as follows:

- If any sample has a TC score of 3, the TC and IC scores of that sample will be selected. In case of multiple samples with TC3, the sample with the maximum IC score will be selected.
- If none of the samples has a TC score of 3, then the IC score of the patient will be the maximum IC score of the multiple samples, and the TC score would be the TC score associated with the sample with the maximum IC score.

5.1.3 NSCLC Pharmacokinetic-Evaluable Population

The NSCLC PK-evaluable population is defined as treated patients with at least one PK sample.

5.1.4 NSCLC Objective Response–Evaluable Population

The NSCLC objective response–evaluable population is defined as the NSCLC efficacy-evaluable population with measurable disease per RECIST v1.1 at baseline and with a minimum of 6 months of follow-up.

5.2 ANALYSIS OF STUDY CONDUCT

The analysis of study conduct will be the same as described for the overall study in Section 3.1.2 but will be performed on the NSCLC safety-evaluable population.

5.3 SAFETY ANALYSES

The safety analyses will be same as described for the overall study in Section 3.1.3 but will be performed on the NSCLC safety-evaluable population. Safety results will be summarized for the overall NSCLC safety-evaluable population and by study treatment dose cohort, as well as by PD-L1 expression using the IHC assay (e.g., TC3 or IC3, TC3 or IC2/3, and TC2/3 or IC2/3 populations).

5.4 EFFICACY ANALYSES

The efficacy analyses will be the same as those described for the overall study in Section 3.1.5 but will performed and summarized for the NSCLC efficacy-evaluable population or NSCLC objective response–evaluable population by PD-L1 expression using the IHC assay (e.g., TC3 or IC3, TC3 or IC2/3, and TC2/3 or IC2/3 population). Of

note, no conclusions may be drawn since the prevalence of PD-L1 status in Study PCD4989g may differ from that of the general population.

In addition to the endpoints specified in Section 3.1.5 specific to NSCLC, the following additional efficacy endpoints will also be summarized.

- ORR and DOR as assessed by the investigator per irRC
- 6-months PFS as assessed by the investigator per irRC)
- 1-year PFS as assessed by the investigator per irRC)

5.5 EXPLORATORY ANALYSES

Confirmed ORR as assessed by the investigator per RECIST v1.1 will be summarized for the NSCLC objective response–evaluable population by subgroups determined by baseline characteristics including histology (squamous vs. non-squamous), mutation status (e.g., EGFR mutation, KRAS mutation, EMLA-ALK rearrangement), ECOG status, smoking status, age, sex, number of prior systemic regimens, bone metastases, and brain metastases.

6. ANALYSIS PLAN SPECIFIC TO RENAL CLEAR CELL PATIENTS IN STUDY PCD4989g

This section specifies analyses that are planned for the RCC patients enrolled in Study PCD4989g and will be included in the CSR.

6.1 ANALYSIS POPULATION

6.1.1 RCC Safety-Evaluable Population

The RCC safety-evaluable population is defined as all enrolled RCC patients who received any amount of atezolizumab on Study PCD4989g.

6.1.2 RCC Efficacy-Evaluable Population

The RCC efficacy-evaluable population is defined as all enrolled clear cell RCC patients who received ≥ 1-mg/kg dose of atezolizumab in Phase I formulation or any amount of atezolizumab in Phase III formulation. When a patient has multiple samples tested or multiple PD-L1 assay results available, the PD-L1 score of the patient will be the maximum PD-L1 score among the multiple samples.

6.1.3 RCC Pharmacokinetic-Evaluable Population

The RCC PK-evaluable population is the same as the RCC safety-evaluable population.

6.1.4 RCC Objective Response–Evaluable Population

The RCC objective response–evaluable population is defined as the RCC efficacy-evaluable population with measurable disease per RECIST v1.1 at baseline.

6.2 ANALYSIS OF STUDY CONDUCT

The analysis of study conduct will be the same those as described for the overall study in Section 3.1.2 but will be performed on the RCC safety-evaluable population.

6.3 SAFETY ANALYSES

The safety analyses will be same as those described for the overall study in Section 3.1.3 but will be performed on the RCC safety-evaluable population. Safety results will be summarized for the overall RCC safety-evaluable population and by study treatment dose.

6.4 EFFICACY ANALYSES

The efficacy analyses will be same as those described for the overall study in Section 3.1.5 but will performed and summarized for the clear cell RCC efficacy-evaluable population by PD-L1 expression levels using IC scores, i.e., IC0/1 vs. IC2/3 and IC0 vs. IC1/2/3). Of note, analyses on the overall clear cell RCC efficacy-evaluable population should be interpreted with caution because of the ascertainment bias introduced from enrollment enrichment per PD-L1 IC status.

In addition to the endpoints specified in Section 3.1.5, the following additional efficacy endpoints specific to RCC will also be summarized:

- ORR and DOR as assessed by the investigator per irRC
- 6-month PFS as assessed by the investigator per irRC

6.5 EXPLORATORY ANALYSES

Confirmed ORR as assessed by the investigator per RECIST v1.1 will be summarized for the RCC efficacy-evaluable population by subgroups determined from baseline characteristics including Memorial Sloan Kettering Cancer Center category, Furhman Grade 4/sarcomatoid histology, number of prior systemic regimens under metastatic setting (0, 1, $\geq$2), and liver metastases at baseline.

7. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE I, OPEN-LABEL, DOSE-ESCALATION STUDY OF THE SAFETY AND PHARMACOKINETICS OF MPDL3280A ADMINISTERED INTRAVENOUSLY AS A SINGLE AGENT TO PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS OR HEMATOLOGIC MALIGNANCIES**
PROTOCOL NUMBER:	PCD4989g
EUDRACT Number:	2011-001422-23
STUDY DRUG:	MPDL3280A
PHASE:	I
INDICATION:	Locally advanced or metastatic solid tumors or hematologic malignancies
IND:	111271
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.

OBJECTIVES

Primary Objectives

- To evaluate the safety and tolerability of MPDL3280A administered by intravenous (IV) infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To determine the maximum tolerated dose (MTD) and to evaluate the dose-limiting toxicities (DLTs) of MPDL3280A when administered as a single agent to patients by IV infusion q3w
- To identify a recommended Phase II dose of MPDL3280A

Secondary Objectives

Pharmacokinetic Objectives

- To evaluate the pharmacokinetics of MPDL3280A when administered as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To characterize the immunogenic potential of MPDL3280A by measuring anti-MPDL3280A antibodies

Activity Objective

- To make a preliminary assessment of the anti-tumor activity of MPDL3280A administered as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies

Appendix 1
Protocol Synopsis (cont'd)

Exploratory Objectives

- To make a preliminary assessment of biomarkers that might act as pharmacodynamic (PD) indicators of anti-tumor activity of MPDL3280A administered as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To make a preliminary assessment of biomarkers that might act as predictors of anti-tumor activity of MPDL3280A administered as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies
- To evaluate overall survival (OS)

Study Design

This Phase I, multicenter, first-in-human, open-label, dose-escalation study will evaluate the safety, tolerability, and pharmacokinetics of MPDL3280A administered as a single agent by IV infusion q3w to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

Approximately eight dose levels ranging from 0.01 to 20 mg/kg (the proposed doses are 0.01, 0.03, and 0.1 mg/kg as single-patient cohorts and 0.3, 1, 3, 10, and 20 mg/kg as $3+3$ cohorts) will be evaluated to determine the MTD or the maximum administered dose (MAD) of MPDL3280A in the dose-escalation stage of the study. Depending on new nonclinical efficacy, clinical safety, and clinical pharmacokinetic (PK) data, additional intermediate dose levels and/or different schedules (with dosing no more frequently than once a week) may be evaluated during the dose-escalation stage after consultation with the study investigators.

Prior to determination of the MTD or MAD, additional patients may be enrolled and treated in expansion cohorts at doses of ≤ 10 mg/kg to better characterize the safety, tolerability, PK variability, and preliminary efficacy of single-agent MPDL3280A. Up to approximately 10 patients with renal cell carcinoma (RCC), 10 patients with melanoma, and 10 patients with non–small cell lung cancer (NSCLC) may be enrolled in each expansion cohort after the 10-mg/kg dose level has been determined to be safe in a minimum of 3 patients.

After determination of the MTD or MAD, additional patients will be enrolled and treated in expansion cohorts at doses and schedules selected to result in a total drug exposure less than or equal to exposures achieved at the MTD or MAD. In order to further characterize the safety of MPDL3280A and to assess biomarkers of tumor activity in different cancer types, the expansion cohorts will include approximately:

- 40 patients with RCC
- 40 patients with NSCLC
- 20 patients with melanoma
- 495 patients with solid tumors or hematologic malignancies may be enrolled. After discussion with the study investigators, prospective enrollment of patients may be based on potential predictive tumor characteristics (e.g., programmed death–ligand 1 positive [PD-L1+] status; in the United States, this applies only in Investigational Device Information (IDI) indications after Investigational Device Information [IDI] submission to the Center for Devices and Radiological Health [CDRH]). See Section 3.1.2 for more details.
- 20 patients with tumors that are amenable to serial biopsy will also be enrolled at the selected dose and schedule. Serial tumor biopsies will be performed for those 20 patients but will be optional for all other patients.

This study will be conducted at approximately 25 sites in the United States and outside the United States. The sample size for this trial will be determined by the dose-escalation rules described in Section 3.1.1 and the number and size of expansion cohorts. Approximately $656–689$ patients will be enrolled in this trial.

Appendix 1
Protocol Synopsis (cont'd)

All patients will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. All adverse events (AEs) will be recorded until 90 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever occurs first. After this period, only ongoing serious adverse events (SAEs) determined by the investigator to be treatment related will be recorded. Additionally, patients with unresolved AEs or abnormal laboratory values deemed related to study treatment may be contacted by telephone for follow-up of these events. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

To characterize the PK properties of MPDL3280A, blood samples will be taken at various timepoints before and after study treatment administration. Blood sampling for PD analyses will be synchronized with select blood draws for the PK studies (see Appendix B). Blood samples will be taken approximately every 30 days (± 14 days) (for up to 120 days) after study treatment has been discontinued because high levels of MPDL3280A may mask detection of anti-therapeutic antibodies (ATAs).

For patients with solid malignancies *(except for prostate cancer)*, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1; see Appendix C) and the immune-related response criteria (irRC) (see Appendix D)
- Do not meet the criteria for continued dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

For patients with prostate cancer, study treatment will be discontinued in patients who meet one of the following:

- *Experience disease progression by Prostate Cancer Response Criteria and confirmed by repeat assessment ≥ 3 weeks after the initial response evaluation (see Appendix E)*
- *Do not meet the criteria for continued dosing after Cycle 1 (see Section 3.1.1)*
- *Are not compliant with the study protocol*

For patients with glioblastoma multiforme (GBM), study treatment will be discontinued in patients who meet one of the following:

- *Experience disease progression by both Revised Assessment in Neuro-Oncology (RANO) Response Criteria (see Appendix F) and irRC (see Appendix D)*
- *Do not meet the criteria for continued dosing after Cycle 1 (see Section 3.1.1)*
- *Are not compliant with the study protocol*

For patients with malignant lymphoma, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by both the Revised International Working Group (IWG) Response Criteria (see Appendix J) and the irRC (see Appendix D)
- Do not meet the criteria for continued dosing after Cycle 1 (see Section 3.1.1)
- Are not compliant with the study protocol

For patients with multiple myeloma, study treatment will be discontinued in patients who meet one of the following:

- Experience disease progression by the International Myeloma Working Group (IMWG) Uniform Response Criteria and confirmed by repeat assessment ≥ 4 weeks after the initial response evaluation (see Appendix K)
- Do not meet the criteria for continued dosing after Cycle 1 (see Section 3.1.1)

- Are not compliant with the study protocol

Patients who experience a DLT will not be allowed to continue receiving study treatment and will be followed for safety (see Section 3.1.1).

Patients will be offered MPDL3280A treatment beyond Cycle 1 as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.6.

Patients who demonstrate radiographic disease progression per RECIST v1.1 for solid tumors; *per RANO Response Criteria for GBM that has not been confirmed by irRC;* per 2007 Revised IWG Response Criteria for malignant lymphoma that has not been confirmed by irRC; *per Prostate Cancer Response Criteria that has not been confirmed by repeat assessment* ;or per IMWG Uniform Response Criteria for multiple myeloma that has not been confirmed by repeat assessment may be considered for continued study treatment if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g., new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Patients who demonstrate confirmed radiographic disease progression according to: both RECIST v1.1 and irRC (solid tumors); both the 2007 Revised IWG Response Criteria and irRC (malignant lymphoma); both the IMWG Uniform Response Criteria and repeat assessment ≥4 weeks after the initial response evaluation (multiple myeloma); *or both RANO Response Criteria and irRC (GBM); or both the Prostate Cancer Response Criteria and repeat assessment ≥3 weeks after the initial response evaluation (prostate cancer)* may be considered for continued study treatment at the discretion of the investigator following discussion with the Medical Monitor, provided they continue to meet all the criteria above and have evidence of clinical benefit.

Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until the death, disease progression, or initiation of further systemic cancer therapy or the study closes, whichever occurs first.

Following treatment discontinuation and follow-up periods, all patients will be followed for survival (see Section 3.1.3) until withdrawal of consent, loss of follow-up, death, or until study termination by the Sponsor, whichever occurs first.

Outcome Measures

Safety Outcome Measures

The safety and tolerability of MPDL3280A administered as a single-agent therapy for patients with locally advanced or metastatic solid tumors or hematologic malignancies will be assessed using the following primary safety outcome measures:

- Incidence and nature of DLTs
- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0

Additionally, safety will be assessed using the following secondary safety endpoints:

Appendix 1
Protocol Synopsis (cont'd)

- Incidence of ATA response and the potential correlation with PK, PD, and safety parameters
- Changes in vital signs and ECG parameters
- Changes in clinical laboratory results
- Number of cycles and dose intensity

Pharmacokinetic Outcome Measures

The following PK data will be derived from the concentration–time data of MPDL3280A when appropriate and when applicable:

- Area under the concentration–time curve (AUC)
- Maximum serum concentration (C_{max})
- Minimum serum concentration (C_{min})
- Clearance (CL)
- Volume at steady state (V_{ss})

Other parameters, such as accumulation ratio, half-life, and dose proportionality, may also be calculated.

Activity Outcome Measures

The activity outcome measures are as follows:

- Best overall response rate with use of RECIST v1.1 and irRC for patients with solid malignancies *(except for prostate cancer)* and disease-specific criteria for patients with *prostate cancer, GBM,* malignant lymphoma and multiple myeloma (see Appendices *E, F, J, and K)*
- Objective response, defined as a complete or partial response
- Duration of objective response, defined as time from the first occurrence of a documented objective response to the time of relapse or death from any cause
- Progression-free survival (PFS), defined as the time from the first study treatment to the first occurrence of progression or death, whichever occurs first

Objective response and disease progression will be determined using RECIST v1.1 (see Appendix C) and irRC (see Appendix D) for patients with solid malignancies *(except for prostate cancer)*. Disease-specific criteria will be used to evaluate objective response and disease progression for patients with *prostate cancer, GBM,* malignant lymphoma or multiple myeloma (see Appendices *E, F, J, and K*).

Exploratory Outcome Measures

The following exploratory activity outcome measures will be assessed:

- Best overall response rate measured from Week 12 (i.e., excluding the Week 6 tumor assessment)
- OS, defined as the time from the first dose of MPDL3280A to the time of death from any cause on study

The following exploratory PD endpoints will be assessed when appropriate:

- Changes in T, B, and natural killer (TBNK) cells numbers (TBNK assay) in blood
- Changes in various T-cell subpopulations in blood (e.g., effector/memory T cells, regulatory T cells, and other T-cell types)
- Identification and profiling of exploratory biomarkers in peripheral blood mononuclear cells (e.g., changes in expression of CD25 or human leukocyte antigen DR [HLA-DR], interferon [IFN]-γ production, and other markers)

- Changes in tumor-infiltrating, $CD8^+$ T cells (and other exploratory markers) in freshly obtained tumor tissue before and on MPDL3280A treatment
- Identification and profiling of exploratory biomarkers in plasma (i.e., interleukin [IL]-2, IFN-γ, and other markers)
- Changes in tumor-infiltrating T-cell activity (measured by expression of granzyme B and other markers) in freshly obtained tumor tissue prior to and during MPDL3280A treatment

The following additional exploratory biomarker endpoints will be assessed when appropriate:

- Enumeration of circulating tumor cell (CTCs) in blood
- Status of PD-L1 (and other exploratory markers) in tumor tissue and in CTCs in blood

Safety Plan

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring.

Because this is the first time MPDL3280A will be administered to humans, all patients will be monitored closely for toxicity. Administration of MPDL3280A will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Additionally, if the first three single-patient cohorts are expanded because of the occurrence of a DLT, dosing of patients in that cohort may be staggered by ≥ 24 hours depending on the nature of the DLT. Dosing of the first 3 patients enrolled in the first $3+3$ cohort (0.3 mg/kg) only will be staggered by ≥ 24 hours. All AEs and SAEs will be recorded during the trial and for up to 90 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. To mitigate potential unknown risks, at least in part, dosing beyond Cycle 1 will be limited to patients who have not developed unacceptable toxicity or had disease progression or who have evidence of potential pseudoprogression.

Study Treatment

The dose levels of MPDL3280A in the Phase I formulation tested in this study include 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 20 mg/kg administered by IV infusion q3w (21 [± 2] days). Additional intermediate dose levels and/or different schedules of MPDL3280A may be tested on the basis of new nonclinical efficacy, clinical safety, and clinical PK data at the time and after discussions with the investigators. The MPDL3280A dose will be based on the patient's weight (in kilograms) measured ≤ 14 days before baseline (Cycle 1, Day 1). It is not necessary to correct dosing on the basis of ideal body weight. For dose levels of 0.01, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg, doses will be prepared by diluting MPDL3280A with diluent (formulation buffer) into an empty sterile vial. For dose levels ≥ 14 mg/kg, no dilution is required.

The dose level of MPDL3280A in the Phase III formulation proposed 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 q3w (21 [± 2] days). MPDL3280A in the Phase III formulation 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 MPDL3280A and PVC or polyolefin infusion materials (bags or infusion lines).

Concomitant Therapy and Clinical Practice

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

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be

substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and beta 2 adrenergic [β_2-adrenergic] agonists; see Appendix F).

Systemic corticosteroids and tumor necrosis factor alpha (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with MPDL3280A but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$ 2 at the discretion of the treating physician after consultation with the Medical Monitor. 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. Planned use of other medications should be discussed with the Medical Monitor.

Patients who use hormonal therapy with gonadotropin-releasing hormone (GnRH) agonists or antagonists for prostate cancer, 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 4.1.2) should continue their use. Males and females of reproductive potential should use highly effective means of contraception. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Statistical Methods

Primary Analysis

The final analysis will be based on patient data collected through study discontinuation. The analyses will all be based on the safety-evaluable population, defined as all patients who receive any amount of MPDL3280A.

Safety Analyses

Safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, changes in vital signs and ECGs, and exposure to MPDL3280A. All patients who receive any amount of MPDL3280A will be included in the safety analyses.

Verbatim descriptions of AEs will be mapped to thesaurus terms. Adverse event data will be listed by study site, dose cohort, treatment arm, patient number, and study day. Events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. In addition, SAEs, including deaths, will be listed separately and summarized.

AEs leading to treatment discontinuation will be listed. AEs leading to the declaration of DLTs will be listed. Patients who withdraw from the study prior to completing the DLT assessment window (Day 21) for reasons other than a DLT will be considered unevaluable for DLT and MTD assessments.

Relevant laboratory and vital signs data will be displayed by time, with NCI CTCAE Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by grade with use of NCI CTCAE v4.0.

Incidence of ATA response and the potential correlation with PK, PD, and safety parameters may be assessed.

Pharmacokinetic and Pharmacodynamic Analyses

Individual and mean serum MPDL3280A concentration versus time data will be tabulated and plotted by dose level. The pharmacokinetics of MPDL3280A will be summarized by estimating total AUC, C_{max}, C_{min}, total CL, V_{ss}, and terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, SD, and coefficient of variation). Interpatient variability and drug accumulation will be evaluated.

Appendix 1
Protocol Synopsis (cont'd)

PD analyses will include assessments of PD biomarkers in both tumor tissue and blood. Changes in PD and potential predictive biomarkers will be listed by dose, cohort, and response status. Additional PK and PD analyses will be conducted as appropriate.

Activity Analyses

The analyses described below will be conducted on the basis of responses as assessed by both RECIST v1.1 (see Appendix C) and irRC (see Appendix D) in patients with solid malignancies; *both RANO Response Criteria (see Appendix F) and irRC (see Appendix D) in patients with GBM*; by both 2007 Revised IWG Criteria *(see Appendix J)* and irRC *(see Appendix D)* in patients with malignant lymphoma; *Prostate Cancer Response Criteria (see Appendix E) and repeat assessment ≥3 weeks after the initial response evaluation in patients with prostate cancer;* and as assessed by IMWG Uniform Criteria *(see Appendix K)* with consecutive assessment ≥4 weeks later in patients with multiple myeloma.

Response assessment data, duration of objective response (for responders), and PFS will be listed for all patients with measurable disease by dose level or tumor type, when appropriate.

Objective response is defined as a complete response or partial response, as determined by investigator assessment and confirmed by repeat assessment ≥4 weeks after initial documentation (confirmation not required for patients with malignant lymphoma). Patients with missing or no response assessments will be classified as non-responders.

Objective response rate will be estimated and summarized by tumor type for the expansion cohorts.

Among patients with an objective response, duration of objective response will be defined as the time from the initial complete or partial response to the time of disease progression or death, whichever occurs first. For patients who do not die or experience disease progression before the end of the study or who are lost to follow-up, duration of objective response will be censored at the day of the last tumor assessment.

PFS is defined as the time from the first day of study treatment with MPDL3280A (Cycle 1, Day 1) until documented disease progression or death, whichever occurs first. For patients who do not have documented progressive disease or death before the end of the study, PFS will be censored at the day of the last tumor assessment.

Summaries will be provided for best overall response rate.

For the evaluation of OS, Kaplan-Meier methodology will be used to estimate the median OS and to construct survival curves. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each tumor type.

Appendix 2
Study Flowchart:

ALL PATIENTS IN DOSE-ESCALATION COHORTS AND FIRST 10 MELANOMA, RCC, OR NSCLC PATIENTS IN EXPANSION COHORTS

	Screening [a]	Cycle 1					Cycles ≥2			Cycles ≥2	Treatment Discon. Visit [b]	Follow-Up
Assessment Window (days)	Days –28 to –1	1	2	4 or 5 [c]	8	15 (±1)	1 [d] (±2)	8 (±2)	15 (±2)	15–21	≤30 Days after Last Dose	
Signed Informed Consent Form(s) [a]	x											
Review of eligibility criteria	x											
Medical, surgical, and cancer histories, including demographic information [e]	x											
EBV, HBV, HCV serology	x											
Concomitant medications [f]	x	x			x	x	x	x [g]	x [g]		x	
Tumor assessment [h]	x									Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy		
CA125 or PSA assessment [i]	x									Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy		
Complete physical examination [j]	x										x	
Limited physical examination [j]		x [k]			x	x	x [k]			x		
ECOG performance status	x	x [k]					x [k]				x	

Appendix 2
Study Flowchart: (cont.)

	Screening [a]	Cycle 1					Cycles ≥2			Cycles ≥2	Treatment Discon. Visit [b]	Follow-Up
Assessment Window (days)	Days –28 to –1	1	2	4 or 5 [c]	8	15 (±1)	1 [d] (±2)	8 (±2)	15 (±2)	15–21	≤30 Days after Last Dose	
Vital signs [l]	x	x			x	x	x				x	
12-lead electrocardiogram [m]	x	x					x [m]				x [o]	
Weight	x [k]	x					x				x	
Height	x											
Local laboratory assessments												
Hematology [n]	x	x [k]	x		x	x	x [k]	x [g]	x [g]		x	
Serum chemistry [o]	x	x [k]	x		x	x	x [k]	x [g]	x [g]		x	
Coagulation panel (aPTT, INR)	x										x	
Urinalysis [p]	x						x [q]				x	
Serum pregnancy test [r]	x											
TSH, free T3, free T4	x										x	
Auto-antibody testing [s]	x						x [q]				x	
Serum sample for ATA assessment [t]		x					x [t]				x	x
Serum sample for PK sampling [u]		x	x	x [c]	x	x	x [u]				x	x
TBNK blood sample [v]	x	x	x			x	x [v]				x	x
Plasma and blood sample for PD biomarkers [w]	x	x	x		x		x [w]				x	x
Adverse events		x	x	x [c]	x	x	x	x [g]	x [g]		x	x
Study treatment infusion [x]		x					x					
Archival tumor tissue specimen or 15 unstained	x											

Appendix 2
Study Flowchart: (cont.)

	Screening [a]	Cycle 1					Cycles ≥2			Cycles ≥2	Treatment Discon. Visit [b]	Follow-Up
Assessment Window (days)	Days –28 to –1	1	2	4 or 5 [c]	8	15 (±1)	1 [d] (±2)	8 (±2)	15 (±2)	15–21	≤30 Days after Last Dose	
slides [y]												
Fresh tumor specimen [z]	x					x				x		x
Survival follow-up [aa]												x

ATA = anti-therapeutic antibody; CA = cancer antigen; Discon = discontinuation; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; FDG = ^{18}fluorodeoxyglucose; HBV = hepatitis B virus; HCV = hepatitis B virus; IMWG = International Myeloma Working Group; irRC = immune-related Response Criteria; IWG = International Working Group; NSCLC = non–small cell lung cancer; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate-specific antigen; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; TBNK = T, B, and natural killer [cells]; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent can be obtained up to 30 days prior to study entry and is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose for a treatment discontinuation visit. After this visit, all adverse events (including serious adverse events and protocol-defined events of special interest), regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever occurs first. Patients will be contacted at 60 and 90 days after the last dose of study treatment to determine whether any new adverse events have occurred. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event.

[c] For patients in the dose-escalation cohorts only.

[d] On Day 1 of Cycle 2, infusion of MPDL3280A can be administered only after completion of the 21-day DLT assessment window, which has a window of +2 days (but not −2 days). All subsequent Day 1 infusions can be administered with a window of ±2 days.

[e] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity.

[f] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications, or medications used since the last documentation of medications will be recorded.

Appendix 2
Study Flowchart: (cont.)

[g] Day 8 of Cycles 2, 3, and 4 only and Day 15 of Cycle 2 only.

[h] Examinations performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at this visit, with use of physical examination and image-based evaluation. For patients with solid malignancies, screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment. If an FDG-PET imaging is performed, PET scans should be acquired 60–75 minutes after administration of the FDG imaging agent at screening and throughout the study, in a fasting patient (>4 hours prior to PET scan) with glucose ≤120 mg/dL. Disease status will be assessed using RECIST v1.1 and irRC. Other methods of assessment of measurable disease according to RECIST v1.1 or irRC may be used. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results have to be reviewed by the investigator before dosing at the next cycle. For patients with other malignancies, please refer to Section 4.5.1. Tumor assessments will be performed every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy. Patients who continue study treatment beyond disease progression should continue to undergo scheduled tumor assessments approximately every 12 weeks until treatment discontinuation.

[i] PSA level for patients with prostate cancer or CA125 level for patients with ovarian cancer or other tumor marker (as appropriate) should be obtained as clinically indicated or with each tumor assessment.

[j] Complete and limited physical examinations are defined in Section 4.5.1.

[k] ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤96 hours before Day 1 of each cycle.

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

[m] For patients in the dose-escalation cohorts, 12-lead ECGs are required as part of the screening assessment, 30 (±15) minutes before and after infusion on Day 1 of Cycle 1; 30 (± 15) minutes before and after infusion on Day 1 of Cycles 2, 3, and 4; and at the treatment discontinuation visit. For patients in the dose-expansion cohorts, digitized, triplicate, 12-lead ECGs will be obtained as part of the screening assessment, 30 (± 15) minutes before and after infusion on Day 1 of Cycle 1, 30 (± 15) minutes before infusion on Day 1 of Cycle 4, and at the treatment discontinuation visit. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[n] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Please refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[o] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. Please refer to Section 4.1.1 for a list of laboratory results

Appendix 2
Study Flowchart: (cont.)

obtained within 14 days prior to the first study treatment.

[p] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[q] On Day 1 of Cycle 3 and every two cycles thereafter.

[r] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1.

[s] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] See Appendix B-1 for details of the ATA collection schedule.

[u] See Appendix B-1 for detailed PK sampling schedule; blood samples should be processed to obtain serum.

[v] See Appendix B-1 for details of the TBNK collection schedule.

[w] See Appendix B-1 for details of the PD sampling schedule.

[x] The initial dose of study treatment will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, 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.

[y] Archival tumor tissue specimen may be obtained from any prior tumor excision or biopsy performed at any time during the course of the patient's illness. Patients may choose to sign a pre-screening consent form to enable the collection of tumor samples for ≥28 days prior to Day 1 of Cycle 1.

[z] Tumor tissue will be obtained by core needle or excisional/punch biopsy from patients who have signed the Optional Research Informed Consent Form. Tumor tissue will also be obtained by excisional/punch biopsy from patients who are undergoing serial biopsies in the dose-expansion cohort. The predose specimen will be obtained after eligibility criteria have been fulfilled. If the predose specimen is evaluable, a subsequent biopsy will then be performed approximately 2 weeks (Cycle 1, Day 15) after first MPDL3280A administration. (The subsequent biopsy may be performed at approximately 1 week [Cycle 1, Day 8] following the first administration of MPDL3280A if there is early sign of response as determined by the investigator.) An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response. See Section 4.5.1 for further details.

[aa] Survival follow-up information will be collected via clinic visits, telephone calls, and/or review of patient medical records approximately every 3 months until patient death, loss to follow-up, or until the study is terminated by the Sponsor. All patients will be followed for survival 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 the study, study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Study Flowchart: (cont.)

STUDY FLOWCHART: ALL EXCEPT THE FIRST 10 MELANOMA, RCC, OR NSCLC PATIENTS IN EXPANSION COHORTS

Assessment Window (days)	Screening [a] Days –28 to –1	All Cycles 1	All Cycles 15–21	Treatment Discon. Visit [b] ≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s) [a]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information [c]	x				
Concomitant medications [d]	x	x		x	
Tumor assessment [e]	x		Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death or initiation of further systemic cancer therapy		
Bone marrow examination (malignant lymphoma and multiple myeloma only) [f]	x		x		
SPEP/IFE, serum FLC, serum β-2 microglobulin (multiple myeloma only) [g]	x		x		
UPEP/IFE from 24-hour urine (multiple myeloma only) [g]	x		x		
Skeletal survey (multiple myeloma only) [h]	x		x		
CA125, or PSA assessment [i]	x		Every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death or initiation of further systemic cancer therapy		
Complete physical examination [j]	x			x	
Limited physical examination [j]		x [k]			
ECOG *or Karnofsky* performance status	x	x [k]		x	
Vital signs [l]	x	x		x	
Triplicate 12-lead electrocardiogram [m]	x	x		x	

Appendix 2
Study Flowchart: (cont.)

Assessment Window (days)	Screening [a] Days –28 to –1	All Cycles 1	All Cycles 15–21	Treatment Discon. Visit [b] ≤30 Days after Last Dose	Follow-Up
B symptoms (malignant lymphoma only)	x		x	x	
Weight	x [n]	x		x	
Height	x				
Local laboratory assessments					
Hematology [n]	x	x [k]		x	
Serum chemistry [o]	x	x [k]		x	
Coagulation panel (aPTT, INR)	x			x	
Urinalysis [p]	x	x [q]		x	
Serum pregnancy test [r]	x				
TSH, free T3, free T4	x			x	
EBV, HBV, HCV, *and HDV* serology [cc]	x				
HBV DNA or HCV RNA test [dd]	*x*	*x*		*x*	
Central laboratory assessments					
Auto-antibody testing [s]	x	x [q]		x	
Serum sample for ATA assessment [t]		x [t]		x	x
Serum sample for PK sampling [u]		x [u]		x	x
TBNK blood sample [v]	x	x [v]		x	x
Plasma and blood sample for PD biomarkers [w]	x	x [w]		x	x
CTC [aa]	x		x	x	
Serum sample for quantitative HBsAg [ee]		*x*		*x*	
Adverse events		x [ff]		x	x
Study treatment infusion [x]		x			

Appendix 2
Study Flowchart: (cont.)

Assessment Window (days)	Screening [a] Days –28 to –1	All Cycles 1	All Cycles 15–21	Treatment Discon. Visit [b] ≤30 Days after Last Dose	Follow-Up
Archival tumor tissue specimen or 15 unstained slides [y]	x				
Fresh tumor specimen [z]	x	x	x		x
Survival follow-up [bb]					x

anti-HBc = antibody to hepatitis B core antigen; ATA = anti-therapeutic antibody; CA = cancer antigen; CTC = circulating tumor cells; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; FDG = ^{18}fluorodeoxyglucose; FLC = free light chain; *HBsAg = hepatitis B surface antigen*; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; *HDV = hepatitis D virus*; irRC = immune-related Response Criteria; NSCLC = non–small cell lung cancer; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate-specific antigen; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; SPEP/IFE = serum protein electrophoresis/immunofixation electrophoresis; TBNK = T, B, and natural killer [cells]; TSH = thyroid-stimulating hormone; UPEP/IFE = urine protein electrophoresis/immunofixation.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent can be obtained up to 30 days prior to study entry and is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests.

[b] Patients will be asked to return to the clinic not more than 30 days after the last dose for a treatment discontinuation visit. After this visit, all adverse events (including serious adverse events and protocol-defined events of special interest), regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever occurs first. Patients will be contacted at 60 and 90 days after the last dose of study treatment to determine if any new adverse events have occurred. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event.

[c] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity.

[d] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[e] Examinations performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used

rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at this visit, with use of physical examination and image-based evaluation. For patients with solid malignancies, screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. CT scans must be used to measure lesions selected for response assessment. If an FDG-PET imaging is performed, PET scans should be acquired 60–75 minutes after administration of the FDG imaging agent at screening and throughout the study, in a fasting patient (>4 hours prior to PET scan) with glucose ≤120 mg/dL. Disease status will be assessed using RECIST v1.1 and irRC. Other methods of assessment of measurable disease according to RECIST v1.1 or irRC may be used. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results have to be reviewed by the investigator before dosing at the next cycle. For patients with other malignancies, please refer to Section 4.5.1. Tumor assessments will be performed every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression, death, or initiation of further systemic cancer therapy. Patients who continue study treatment should continue to undergo scheduled tumor assessments approximately every 12 weeks until treatment discontinuation.

[f] A bone marrow examination (aspirate and trephine biopsy) must be performed at screening for patients with malignant lymphoma and multiple myeloma. A repeat aspirate and biopsy at Cycle 4, Days 15–21 are also required to assess response. In patients with malignant lymphoma or multiple myeloma, a repeat bone marrow biopsy and aspirate are necessary to confirm a complete clinical response if physical examination and CT scan demonstrate a clinical response.

[g] For multiple myeloma patients, SPEP/IFE, serum FLC, serum β-2 microglobulin, and UPEP/IFE from 24-hour urine will be performed at screening and with each tumor assessment timepoint (i.e., end of Cycles 2, 4, 6, 8, 12, 16, 20, 24, 28 and 32 or as clinically indicated).

[h] For multiple myeloma patients, skeletal survey (a set of full body X-rays) will be performed at screening, Cycle 4, Days 15–21, and at any time needed to confirm complete response. CT or MRI scans may also be included as needed for the measurement of soft tissue plasmacytomas.

[i] PSA level for patients with prostate cancer, CA125 level for patients with ovarian cancer, or other tumor marker (as appropriate) should be obtained as clinically indicated or with each tumor assessment.

[j] Complete and limited physical examinations are defined in Section 4.5.1.

[k] ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤96 hours before Day 1 of each cycle.

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

[m] For patients in the dose-expansion cohorts, digitized, triplicate, 12-lead ECGs will be obtained as part of the screening assessment, 30 (±15) minutes before and after infusion on Day 1 of Cycle 1, 30 (±15) minutes before infusion on Day 1 of Cycle 4, and at the

treatment discontinuation visit. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[n] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[o] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[p] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[q] On Day 1 of Cycle 3 and every two cycles thereafter.

[r] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1.

[s] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[t] See Appendix B-2 for details of the ATA collection schedule.

[u] See Appendix B-2 for detailed PK sampling schedule; blood samples should be processed to obtain serum.

[v] See Appendix B-2 for details of the TBNK collection schedule.

[w] See Appendix B-2 for details of the PD sampling schedule.

[x] The initial dose of study treatment will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

[y] Archival tumor tissue specimen may be obtained from any prior tumor excision or biopsy performed at any time during the course of the patient's illness. Patients may choose to sign a pre-screening consent form to enable the collection of tumor samples for ≥ 28 days prior to Day 1 of Cycle 1.

[z] Tumor tissue will be obtained by core needle or excisional/punch biopsy from patients who have signed the Optional Research Informed Consent Form. Tumor tissue will also be obtained by excisional/punch biopsy for patients who are undergoing serial biopsies in the dose-expansion cohort. The predose specimen will be obtained after eligibility criteria have been fulfilled. If the predose specimen is evaluable, a subsequent biopsy will then be performed approximately 2 weeks (Cycle 1, Day 15) after the first MPDL3280A administration. (The subsequent biopsy may be performed at approximately 1 week [Cycle 1, Day 8] following the first administration of MPDL3280A if there is early sign of response as determined by the investigator.) An additional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression or response. See Section 4.5.1 for further details.

[aa] CTC will be assessed in blood of patients at screening (excluding patients with hematologic malignancies), Cycle 1, Day 1 (before dosing), Cycle 3, Day 1 (before dosing), at the time of radiographic progression or response, and at the treatment discontinuation visit.

[bb] Survival follow-up information will be collected via clinic visits, telephone calls, and/or review of patient medical records approximately every 3 months until patient death, loss to follow-up, or until the study is terminated by the Sponsor. All patients will be followed for

Appendix 2
Study Flowchart: (cont.)

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

[cc] *HDV serology at screening is required only for patients with HCC infected with HBV.*

[dd] *HBV DNA test is required before Cycle 1, Day 1 for non-HCC patients who have positive serology for anti-HBc at screening. HBV DNA test at Day 1 of each cycle and treatment discontinuation visit is required for patients with HCC with positive HBsAg at screening. HCV RNA test is required before Cycle 1, Day 1 for non-HCC patients who have positive serology for anti-HCV at screening. HCV RNA test at Day 1 of each cycle and treatment discontinuation visit is required for patients with HCC with positive anti-HCV at screening.*

[ee] *Quantitative HBsAg will be assessed at a central laboratory in serum of patients with HCC who have a positive HBsAg at screening, at Day 1 of each cycle, and at the treatment discontinuation visit.*

[ff] *Adverse events will be checked additionally at Cycle 1, Day 1 and Cycle 1, Day 8 for the first approximately 50 patients enrolled into the dose expansion cohorts after the implementation of Protocol Amendment 7.*

Appendix 3
Study PCD4989g Anti-Therapeutic Antibody, TBNK, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Except the First 10 Melanoma, RCC, or NSCLC Patients in Expansion Cohorts

Study Visit	Time	Sample	
		Dose-Escalation Cohorts	Expansion Cohorts
Screening	At visit	TBNK MPDL3280A PD [a] CTC	TBNK MPDL3280A PD [a] CTC
Cycle 1, Day 1	Predose	ATA MPDL3280A PK TBNK MPDL3280A PD [a] CTC	ATA MPDL3280A PK TBNK MPDL3280A PD [a]
	30 min (±10 min) after end of MPDL3280A infusion	MPDL3280A PK MPDL3280A PD [b]	MPDL3280A PK MPDL3280A PD [b]
Cycle 1, Day 2	24 hr (±6 hr) after end of MPDL3280A infusion on Day 1	MPDL3280A PK TBNK MPDL3280A PD [b]	MPDL3280A PK TBNK MPDL3280A PD [b]
Cycle 1, Day 4	72 hr (±12 hr) after end of MPDL3280A infusion on Day 1	MPDL3280A PK	NA
Cycle 1, Day 8 (±1 day)	At visit	MPDL3280A PK MPDL3280A PD [b]	MPDL3280A PK MPDL3280A PD [b]
Cycle 1, Day 15 (±1 day)	At visit	MPDL3280A PK TBNK	MPDL3280A PK TBNK
Cycles 2, 3, 4, 5, and 7, Day 1 (±2 days)	Predose	ATA (Cycles 2 and 4 only) MPDL3280A PK [c] TBNK (Cycles 2, 3, and 4 only) MPDL3280A PD [d] CTC (Cycle 3 only)[e]	ATA (Cycles 2 and 4 only) MPDL3280A PK [c] TBNK (Cycles 2, 3, and 4 only) MPDL3280A PD [d] CTC (Cycle 3 only)[e]
	30 min (±10 min) after end of MPDL3280A infusion	MPDL3280A PK [c]	MPDL3280A PK (Cycles 2, 3, and 4 only) [c]
Cycles 8, 10,12, 14, and 16 , Day 1 (±2 days)	Predose	ATA (Cycles 8 and 16 only) MPDL3280A PK [c]	ATA (Cycles 8 and 16 only) MPDL3280A PK (Cycles 8 and 16 only) [c]
Cycles ≥17, Day 1 (±2 days)	Predose	MPDL3280A PK (Cycles 17 *and* 20 and *every eight cycles thereafter*) ATA (Cycles 17 *and* 20 and *every eight cycles thereafter*)	MPDL3280A PK (Cycles 17 and 20 and every eight cycles thereafter ATA (Cycles 17 and

Appendix 3
Study PCD4989g Anti-Therapeutic Antibody, TBNK, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Except the First 10 Melanoma, RCC, or NSCLC Patients in Expansion Cohorts (cont.)

Study Visit	Time	Sample	
		Dose-Escalation Cohorts	Expansion Cohorts
		TBNK (Cycles 17 *and 32* only) MPDL3280A PD (Cycles 17 and 32 only) [h]	20 and every eight cycles thereafter) TBNK (Cycles 17 and 32 only) MPDL3280A PD (Cycles 17 and 32 only)[h]
Treatment discontinuation visit	At visit	ATA MPDL3280A PK TBNK MPDL3280A PD [a] CTC[e]	ATA MPDL3280A PK TBNK MPDL3280A PD [a] CTC[e]
Post–treatment discontinuation visits [f, g]	At visit	ATA MPDL3280A PK TBNK [g] MPDL3280A PD [a,g]	ATA MPDL3280A PK TBNK [g] MPDL3280A PD [a,g]
At time of fresh biopsy (pre-treatment and on-treatment or at progression)	At visit	TBNK MPDL3280A PD [a]	TBNK MPDL3280A PD [a]

ATA = anti-therapeutic antibody; CTC = circulating tumor cells; NA = not applicable; NSCLC = non–small cell lung cancer; PD = pharmacodynamic (plasma, whole blood, or peripheral blood mononuclear cells [PBMCs] for PD biomarkers); PK = pharmacokinetic; RCC = renal cell carcinoma; TBNK = T, B, and natural killer [cells].

[a] Plasma, whole blood, and PBMCs.

[b] Plasma only.

[c] In patients who undergo intrapatient dose escalation after Cycle 4 (i.e., starting with Cycle 5, Day 1), PK samples should also be obtained before dosing and 30 minutes (± 10 minutes) after end of MPDL3280A infusion at Cycles 6 and 8.

[d] Cycles 2 and 3: plasma, whole blood, and PBMCs. Cycles 4 and 7: plasma. Cycle 5: whole blood and PBMCs.

[e] CTC will be assessed at screening (excluding patients with hematologic malignancies), Cycle 1, Day 1 (before dosing), Cycle 3, Day 1 (before dosing), at the time of radiographic progression or response, and at the treatment discontinuation visit.

f For patients who discontinue the study treatment, ATA and PK samples are to be obtained every 30 days (± 14 days) (for up to 120 days) after the last dose of study treatment unless the patient dies or withdraws consent or the study closes. ATA and PK samples collected at the treatment discontinuation visit will be counted as the first collection.

[g] For patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) and continue to undergo scheduled tumor assessments approximately every 12 weeks. PD samples are to be obtained at disease progression if determined from follow-up tumor assessment.

[h] Plasma and PBMCs.

Appendix 3
Study PCD4989g Anti-Therapeutic Antibody, TBNK, Pharmacodynamic, and Pharmacokinetic Sampling Schedule: All Except the First 10 Melanoma, RCC, or NSCLC Patients in Expansion Cohorts (cont.)

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[i] *For the first approximately 50 patients enrolled after implementation of Protocol Amendment 7 only.*