SUMMARY OF CHANGES

For Protocol Version 9
HCC #: 16-153

Previous Protocol Date: 6/18/2020
Current Protocol Date: 8/17/2020

#	Section	Page(s)	Change
1	7.3.2.4	39	Removed statement: "…*or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 90…"* Justification for the change: The Female pregnancy information is needed for 5 months per the most recent version of the US Package Insert for atezolizumab.
2	7.3.4	41	Changed from: *Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, and systemic inflammatory response syndrome* Changed to: *Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, macrophage activating syndrome and hemophagocytic lymphohistiocytosis.* Justification for the change: This has been updated for consistency with the most recent version of the US Package Insert for atezolizumab.
3	7.4	42	Replaced the safety reporting email with a Hotline Number for the reports. Justification for the change: The sponsor changed the manner in which safety reporting is conducted.

TITLE: A phase II clinical trial evaluating the efficacy of atezolizumab in advanced non-small cell lung cancer (NSCLC) patients previously treated with PD-1-directed therapy

HCC #:	16-153
BB-IND#:	N/A
Phase:	II
Version:	7
Version Date:	8/17/2020
Investigational Agent:	Atezolizumab
Commercial Agent:	N/A

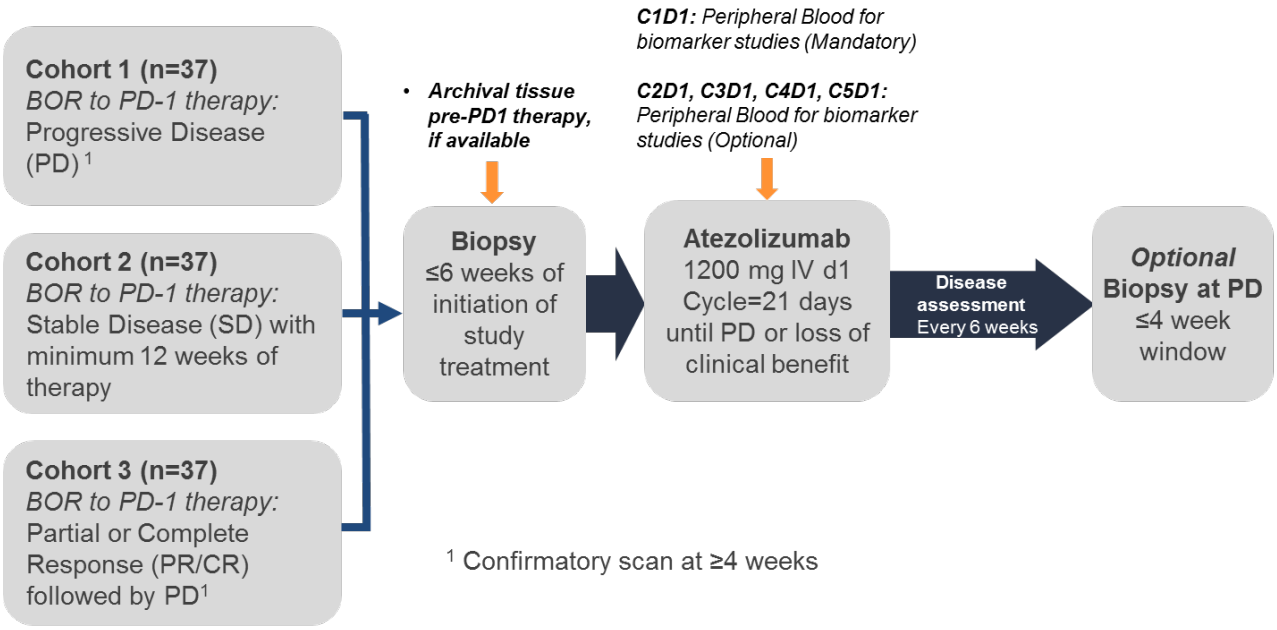
Sponsor-Investigator: Liza C. Villaruz, MD
UPMC Cancer Pavilion, 5th floor
5150 Centre Avenue
Pittsburgh, PA 15232
Email: villaruzl@upmc.edu
Phone: 412-648-6578
Fax: 412-648-6579

Biostatistician: Daniel Normolle, PhD
325 Sterling Plaza, Suite 325
201 N. Craig Street
Pittsburgh, PA 15213
Email : dpn7@pitt.edu
Phone : 412-383-1591

Source of Support: Genentech

SCHEMA

This is a phase II clinical trial aimed at evaluating the efficacy of PD-L1 inhibition with atezolizumab in advanced squamous and non-squamous NSCLC patients previously treated with anti-PD-1 therapy with either nivolumab or pembrolizumab. The kinetics of response to immune checkpoint inhibition can be variable and complicated by an initial increase in tumor burden or the appearance of new lesions, followed by disease response (pseudo-progression). In order to account for the variability of response kinetics to PD-1 directed therapy, patients will be enrolled in 3 parallel cohorts based on the best overall response (BOR) to PD-1 directed therapy.



Collection of archival tumor specimens pre-PD-1 directed therapy (if available), mandatory biopsies at the time of enrollment and optional re-biopsy at the time of disease progression on atezolizumab, as well as mandatory collection of peripheral blood on C1D1 and optional collection of peripheral blood on day 1 of C2 through C5, will be performed for completion of translational studies aimed at identifying candidate biomarkers of response and mediators of resistance to PD-1 and PD-L1 directed therapies.

Primary Objective:

- To estimate the BOR of atezolizumab in patients previously treated with PD-1 directed therapy, in each of three parallel cohorts defined by BOR to PD-1 directed therapy.

Secondary Objectives:

- To estimate the duration of response (DOR) of atezolizumab in patients previously treated with anti-PD-1 therapy, based on the BOR to PD-1 directed therapy.
- To estimate the progression-free survival (PFS) of atezolizumab in patients previously treated with anti-PD-1 therapy, based on the BOR to PD-1 directed therapy.
- To estimate the overall survival (OS) of atezolizumab in patients previously treated with

anti-PD-1 therapy, based on the BOR to PD-1 directed therapy.

- To estimate the safety of atezolizumab in patients previously treated with anti-PD-1 therapy, as determined by grade ≥ 3treatment related adverse events.

Exploratory objectives:

- To understand mechanisms of immune escape and assess biomarkers of response, including but not limited to PD-L1 expression.

Treatment Regimen

Atezolizumab will be given on day 1 of a 21-day cycle at 1200 mg IV. Radiographic assessments for disease response will occur every 6 weeks while on treatment. Confirmatory scans should be obtained ≥ 4 weeks following initial documentation of objective response or progressive disease on atezolizumab therapy.

Statistical Methods

Primary Objective:

- For each cohort, a BOR rate of 15% would be promising compared to a null rate of 2%. The target enrollment is 37 evaluable patients within each cohort. A stopping rule for futility is implemented using Simon's optimal two-stage design, if none of the first 11 evaluable patients within a cohort have a confirmed objective response. Accrual may continue during follow-up for these patients. If 1 or more responses are observed in the first 11 evaluable patients in a cohort, an additional 26 patients will be enrolled. Importantly, if one cohort meets criteria for futility in stage 1, the other cohort(s) may proceed to stage 2, if indicated. A promising study result would be if 3 or more responses are seen at the conclusion of stage 2. This design has 80% power for each cohort to detect a true response rate of 15% (compared with a null rate of 2%). The one-sided type 1 error rate is 0.05 for each cohort.

Secondary Objectives:

- For patients experiencing complete or partial tumor responses, the distribution of response duration, measured as the time from complete response (CR) or partial response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started) will be characterized by the median and quartiles, and graphical display of Kaplan-Meier estimates of response duration, separately for each cohort and for all responders.

- Progression-free survival (PFS, months from start of treatment to time of progression, death or last radiographic assessment without PD, whichever occurs first) and overall survival (OS, months from first study treatment to death or last contact) will be summarized separately for each cohort. The PFS function and median PFS will be

estimated by the Kaplan-Meier method, with a 90% confidence interval using the Greenwood variance formula applied to log-transformed survival.

- Adverse events will be graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) version 4. Adverse events of grade 3 or greater determined to be possibly, probably or definitely related to treatment, or that result in dose holds or reductions, will be collected and reported. Adverse events and serious adverse events will be tabulated in order of prevalence, with the highest grade reported by each patient. The number and percent of subjects reporting adverse events will be summarized by category (i.e., "Blood and lymphatic system disorders"), for the most common adverse event subcategories (i.e., "anemia"), and for serious adverse events (defined in section 7.2). Narratives of all serious adverse events and deaths on-study will be provided. All safety data will be tabulated separately by cohort, and for the full study sample.

Exploratory Objectives:

- PD-L1 expression will be measured in tissue from a mandatory biopsy conducted after discontinuation of the prior therapy and before initiation of study therapy. The primary analysis will examine associations between PD-L1 expression and best overall response by RECIST 1.1, for all cohorts combined. These two ordinal variables (immunohistochemistry and response) will first be described graphically in a mosaic plot, which may suggest a clinically relevant dichotomization of PD-L1 expression and/or best overall response. Further analysis may use generalized linear model approaches for ordinal regression, or treat response as dichotomous or continuous, with limited models fit to avoid "p-hacking".

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- To estimate the BOR of atezolizumab in patients previously treated with PD-1 directed therapy, in each of three parallel cohorts defined by BOR to PD-1 directed therapy.

1.2 Secondary Objectives

- To estimate the duration of response (DOR) of atezolizumab in patients previously treated with anti-PD-1 therapy, based on the BOR to PD-1 directed therapy.
- To estimate the progression-free survival (PFS) of atezolizumab in patients previously treated with anti-PD-1 therapy, based on the BOR to PD-1 directed therapy.
- To estimate the overall survival (OS) of atezolizumab in patients previously treated with anti-PD-1 therapy, based on the BOR to PD-1 directed therapy.
- To estimate the safety of atezolizumab in patients previously treated with anti-PD-1 therapy, as determined by grade ≥ 3treatment related adverse events.

1.3 Exploratory Objectives

- To understand mechanisms of immune escape and assess biomarkers of response, including but not limited to PD-L1 expression.

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related deaths worldwide with an estimated incidence of 1.6 million cases resulting in 1.4 million deaths in annually (Jemal et al., 2011). Non-small-cell lung cancer (NSCLC) represents 80-85% of cases (Jemal et al., 2011). The majority of NSCLC patients present with advanced or metastatic disease, which is not amenable to surgical resection. Platinum-based combination chemotherapy has reached a therapeutic plateau with a median overall survival (OS) of 7.4 to 9.9 months. The recent advances in the treatment of NSCLC have come from the recognition that NSCLC is not a single disease entity but rather a collection of distinct molecularly driven neoplasms. This principle is supported by the seminal finding that sensitizing *epidermal growth factor receptor* (*EGFR*) mutations are present in about 10-15% of lung cancers and are targetable with the FDA approved EGFR tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib and afatinib) (Jemal et al., 2011; Ettinger et al., 2010). Additionally, translocations involving the *anaplastic lymphoma kinase* (ALK) are found in 5-8% of adenocarcinomas of the lung and can be targeted by several ALK TKIs (crizotinib, ceritinib and alectinib) (Somasundaram et al., 2014; Kris et al., 2014).

The therapeutic landscape of previously treated advanced NSCLC in the absence of an actionable oncogenic driver has shifted from a cytotoxic approach to modulation of the immune checkpoints. The programmed death 1 receptor (PD-1) is expressed on activated T-cells and

engaged by the programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) that are expressed on tumor cells and infiltrating immune cells (Pardoll et al., 2012). In NSCLC, tumor PD-L1 expression is prevalent and PD-1 interaction with the ligands, PD-L1 and PD-L2, inhibits cell activation and promotes tumor recognition and elimination (Chen et al., 2012; Velcheti et al., 2014). Nivolumab is a fully human IgG4 programmed death 1 immune checkpoint antibody inhibitor that disrupts PD-1-mediated signaling and restores antitumor immunity (Brahmer et al., 2010; Topalian et al., 2012). In phase I studies, nivolumab monotherapy showed a durable anti-tumor activity in NSCLC (Brahmer et al., 2010; Topalian et al., 2012; Gettinger et al., 2015) including NSCLC of squamous and non-squamous histology.

In a landmark prospective randomized phase III study (CheckMate017) (Brahmer et al., 2015), two hundred and seventy-two patients with advanced squamous NSCLC previously treated with platinum based chemotherapy were treated with nivolumab (3 mg/kg every two weeks) versus docetaxel (75 mg/m^2 every three weeks). The primary endpoint was overall survival, and PD-1 inhibition with nivolumab was found to be associated with an improvement in median overall survival to 9.2 months versus 6.0 months with docetaxel (HR 0.59; P<0.001). The response rate with nivolumab was 20% versus 9% with docetaxel (p = 0.008), and the median progression-free survival was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR of 0.62; P < 0.001). Additionally, PD-L1 protein expression utilizing the 28-8 antibody (Dako) was evaluated retrospectively in pre-treatment (archival or recent) tumor-biopsy specimens. Interestingly, PD-L1 expression was not predictive of benefit. Given the results of this study, nivolumab was approved in March of 2015 for treatment of advanced squamous NSCLC previously treated with a platinum based therapy regardless of PD-L1 expression.

A phase III study (CheckMate057) examined the effect of nivolumab (3 mg/kg every two weeks) versus docetaxel (75 mg/m^2 every three weeks) in a group of five hundred and eighty-two patients with non-squamous advanced NSCLC previously treated with platinum-doublet chemotherapy. The primary endpoint was overall survival and was found to be longer in patients treated with nivolumab versus docetaxel with a median overall survival of 12.2 months in the nivolumab arm versus 9.4 months in the docetaxel arm (HR 0.73; P=0.002). The objective response rate was also higher with nivolumab (19%) versus docetaxel (12%; P=0.02) (Borghaei et al., 2015). Similar to Brahmer et al., PD-L1 protein expression was assessed retrospectively in archival or recent tumor biopsy specimens utilizing the 28-8 antibody (Dako). In the group with ≥10% PD-L1 expression treated with nivolumab, the objective response was 37% (95% CI 27 to 48). In contrast, in the group ≥10% PD-L1 expression treated with docetaxel, the objective response rate was 13% (95% CI 6 to 22). Amongst patients whose tumors expressed PD-L1, nivolumab nearly doubled median overall survival as compared with docetaxel (Borghaei et al., 2015).

Pembrolizumab is a highly selective humanized, IgG4 monoclonal antibody against PD-1. Recently, Pembrolizumab given at 2 mg/kg every 3 weeks was granted accelerated approval for the treatment of metastatic NSCLC patients whose tumors express PD-L1 with disease progression after platinum-based chemotherapy. The KEYNOTE-010 compared the administration of pembrolizumab at 2 mg/kg every three weeks versus pembrolizumab at 10 mg/kg every three weeks versus standard of care treatment docetaxel at 75 mg/m^2. Patients in this large multi-center phase II/III study had advanced NSCLC with PD-L1 expressing tumors by the 22C3 antibody (Dako). Both squamous and non-squamous histologies were included. In this trial, one thousand and thirty-four patients were randomized 1:1:1 to receive pembrolizumab at 2

mg/kg, pembrolizumab at 10 mg/kg or docetaxel at 75 mg/ m^2 (Herbst et al., 2015). In this clinical trial, pembrolizumab at either dose significantly improved OS compared with docetaxel, an9ffectt which was particularly pronounced in patients with tumors with ≥ 50% PD-L1 expression. In this clinical trial, the median overall survival was 10.4 months (95% CI 9.4 -11.9) with pembrolizumab at 2 mg/kg, 12.7 months (95% CI 10.0 – 17.3) with pembrolizumab at 10 mg/kg and 8.5 months (95% CI 7.5 – 9.8) with docetaxel. Among patients with tumors with at least 50% PD-L1 expression, the median overall survival was 14.9 months (95% CI 10.4 – NR) in the pembrolizumab 2 mg/kg group, 17.3 months (95% CI 11.8 – NR) in the pembrolizumab10 mg/kg group and 8.2 months (95% CI 6.4 – 10.7) for the docetaxel group (Herbst et al., 2015).

Durvalumab is a human IgG1 monoclonal antibody that blocks both PD-L1 binding to PD-1 and CD80. In a phase I/II study of durvalumab in patients with multiple solid tumor types, 200 NSCLC patients were evaluable for response (112 non-squamous and 88 squamous histology), in whom the ORR was 16% with a disease control rate of 42% at 12 weeks. In patients with PD-L1 positive disease (determined using the SP263 antibody IHC assay, Ventana), the ORR was 27% (95% CI 18.2-38.2) compared with 5% (95% CI 1.8-12.2) in PD-L1 negative patients (Rizvi et al. 2015).

Atezolizumab is a fully humanized monoclonal antibody of IgG1 isotype against programmed death ligand-1. A phase II study (POPLAR) randomized previously treated NSCLC patients to atezolizumab given 1200 mg every three weeks versus docetaxel at 75 mg/m^2 (Spira et al, 2015; Vansteenkiste et al, 2015), stratified by PD-L1 immune cell (IC) status. PD-L1 expression was scored on a scale of 0 to 3 on both the tumor cells (TC) and the immune cells (IC) by IHC using the SP142 antibody assay (Ventana). PD-L1 inhibition with atezolizumab was associated with a trend toward improved efficacy in patients with high PD-L1 expressing tumors (TC3 or IC3) with a median OS of 15.5 months in the atezolizumab group and 11.1 months in the docetaxel group (HR 0.49; P=0.068). In patients with moderate to high PD-L1 expression (TC2/3 or IC2/3), there was a statistically significant improvement in median OS from 7.4 months with docetaxel to 15.1 months with atezolizumab (HR 0.54; P=0.014). An OS benefit was also seen in patients with any PD-L1 expression (TC1/2/3 or IC1/2/3; median OS 15.5 months versus 9.2 months, atezolizumab versus docetaxel, respectively, HR 0.59, P=0.005). Patients with the lowest PD-L1 expression levels (TC0 and IC0) did not appear to have any benefit from atezolizumab with a median OS of 9.7 months in both the atezolizumab and docetaxel arms (HR 1.04; P=0.871) (Spira et al., 2015; Vansteenkiste et al, 2015). The safety of atezolizumab in 142 patients treated on this study was consistent with prior clinical studies; patients receiving atezolizumab experienced fewer grade 3 and 4 treatment related adverse side effects (ASEs) compared with docetaxel (11% versus 39%, respectively), and fewer grade 5 treatment related ASEs (1% versus 2%, respectively). Adverse events occurring in ≥ 5% patients treated with atezolizumab included anorexia, dyspnea, fever, arthralgias, insomnia, pneumonia and hypothyroidism.

BIRCH is a single-arm phase II clinical trial of atezolizumab in treatment naïve and previously treated NSCLC patients with at least moderate PD-L1 tumor staining (TC2/3 or IC2/3) (Besse et al., 2015). In previously untreated patients, the ORR was 26% (95%CI 16-39) in patients with high PD-L1 (TC3 or IC3) expressing tumors and 19% (95% CI 13-27) in patients with moderate to high PD-L1 (TC2/3 or IC2/3) expressing tumors. In the second line setting, atezolizumab was associated with an ORR of 24% (95% CI 17-32) in previously treated patients with high PD-L1 expressing tumors and 17% in (95% CI 13-22) in patients with moderate to high PD-L1

expressing tumors. In patients receiving atezolizumab in the 3rd line and beyond, the ORR was 27% (95% CI 19-36) in patients with high PD-L1 expressing tumors and 17% (95% CI 13-23) in patients with moderate to high PD-L1 expressing tumors (Besse et al. 2015). In 659 safety evaluable patients, 11% patients experienced grade 3 and 4 treatment related ASEs, similar to prior studies. The most common treatment related ASEs were fatigue, diarrhea, nausea, pruritus, fever, anorexia, weakness, rash, and arthralgia.

FIR is a single arm phase II clinical trial in which patients with moderate to high PD-L1 expressing tumors (TC2/3 or IC 2/3) were treated with atezolizumab in the 1st line and in the 2nd line and beyond (Chaft et al., 2015). Atezolizumab was associated with an ORR of 29% (95% CI 14-48) in patients treated in the 1st line; the ORR was 29% in patients with high PD-L1 expressing tumors (TC3 and/or IC3). In previously treated patient without brain metastases, atezolizumab was associated with an ORR of 17% (95% CI 10-27%); the ORR in patients with high PD-L1 expressing tumors was 26% (95% CI 13-43). In previously treated patients with treated brain metastases, the ORR was 23% (95% CI 5-54); in the ORR in patients with high PD-L1 expressing tumors was 25% (95% CI 3-65). In 137 safety evaluable patients, 15% patients experienced grade 3 and 4 treatment related ASEs, similar to prior studies. The most common treatment related ASEs were fatigue, nausea, anorexia, diarrhea, fever, pruritus, arthralgia, myalgias, vomiting and anima.

In February of 2015, atezolizumab received "Breakthrough Therapy" designation from the Federal Drug Administration for the treatment of NSCLC that expresses PD-L1 with disease progression during or after standard platinum-based chemotherapy or targeted therapy.

2.2 Atezolizumab

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human 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 (TecentriqTM) is approved in the United States for the treatment of locally advanced or metastatic urothelial cancer (UC) and non-small cell lung cancer which has grown on or after chemotherapy. Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

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

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

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

Clinical Safety

The presented safety data for atezolizumab have been derived mainly from the treatment of patients in Phase Ia Study PCD4989g. As of 10 May 2014, atezolizumab has been administered to approximately 775 patients with solid and hematologic malignancies. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) was established. Fatigue was the most frequently reported adverse event (AE).

Adverse Events

The following safety data are from PCD4989g, in which atezolizumab is being used as single-agent therapy in patients with locally advanced or metastatic solid tumors or hematologic malignancies. In 412 treated patients, 97.1% reported an AE while on study. Of these Aes, 48.8% 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). The most frequently observed Aes (occurring in $\geqslant$ 10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, and upper respiratory tract infection.

Grade $\geqslant$ 3 Aes were reported by 199 of 412 patients (48.3%). There were 51 patients (12.4%) who reported Grade $\geqslant$ 3 Aes that were assessed as related to study drug by the investigators. The most frequently reported related Grade $\geqslant$ 3 Aes included fatigue (5 patients [1.2%]), increased ALT and increased AST (each reported in 4 patients [1.0%]); and asthenia, autoimmune hepatitis, and hypoxia (each reported in 3 patients [0.7%]).

Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated Aes have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness. Expected adverse drug reactions associated with atezolizumab include the following: hepatitis/transaminitis, hypothyroidism, infusion-related reactions (IRRs), pneumonitis, influenza-like illness, and dermatologic reactions. Potential adverse drug reactions include the following: anti-therapeutic

antibodies (ATAs), colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion.

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 clearance (CL) and the mean volume at steady state (Vss) had a range of 3.20-4.43 mL/kg and 48.1-64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of 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 10-20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and Aes or IRRs has been observed.

2.3 Rationale

The therapeutic landscape of previously treated advanced NSCLC in the absence of an actionable oncogenic driver has shifted from a cytotoxic approach to modulation of the immune checkpoints. It is notable that while inhibition of the PD-1 axis is associated with improved response rates versus cytotoxic therapy in patients with previously treated NSCLC, the majority of patients will not benefit from an objective response. It is also notable that anti-PD-1 and anti-PD-L1 antibodies block distinct inhibitory pathways, possibly resulting in different clinical outcomes. While anti-PD-1 antibodies block PD-1 binding to PD-L1 and PD-L2, they do not affect the inhibitory signal occurring upon the PD-L1/B7.1 interaction. Conversely, while anti-PD-L1 antibodies block PD-L1 binding to B7.1 and PD-1, they do not impede the inhibitory signaling provided by the interaction of PD-1 and PD-L2. This clinical trial is critical to evaluating the efficacy of sequencing PD-L1 inhibition in patients with stable or progressing disease on PD-1 directed therapy and to the identification of candidate biomarkers of response and resistance to PD-1/PD-L1 directed therapies.

The kinetics of response to immune checkpoint inhibition can be variable and complicated by an initial increase in tumor burden or the appearance of new lesions, followed by disease response (pseudo-progression). In 129 pretreated advanced NSCLC patients receiving nivolumab 1, 3, or 10 mg/kg every 2 weeks, tumor burden was assessed by RECIST (version 1.0) every 8 weeks (Gettinger et al., 2015). Among 22 patients (17%) with objective responses, estimated median response duration was 17.0 months. An additional six patients (5%) had unconventional immune-pattern responses (Figure 1). In order to account for the variability of response kinetics to PD-1 directed therapy, patients will be enrolled in 3 parallel cohorts based on the best overall response (BOR) to PD-1 directed therapy with either nivolumab or pembrolizumab.

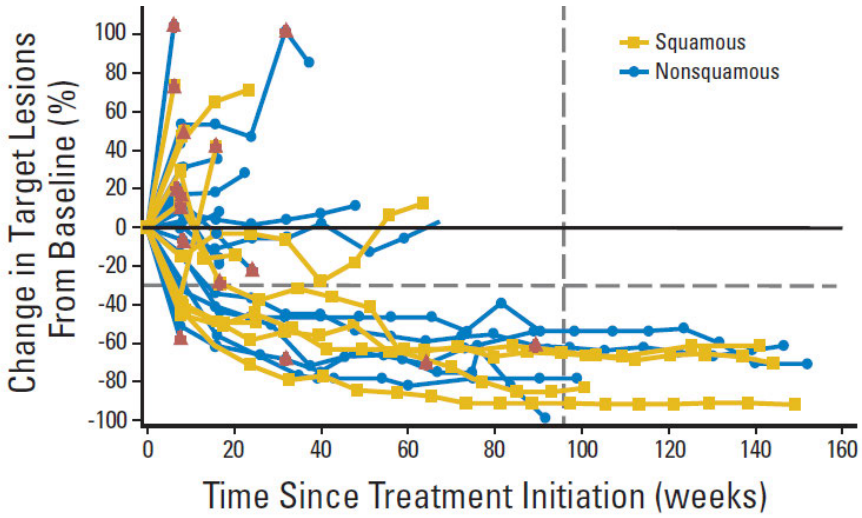


Figure 1. Tumor burden kinetics in patients with NSCLC treated with nivolumab 3 mg/kg, in whom baseline tumor measurements are standardized to zero. Red triangles indicate first occurrence of new lesion. Horizontal dashed line at 30% indicates threshold for defining objective response (partial tumor regression) in absence of new lesions or nontarget disease progression, according to RECIST (version 1.0); vertical dashed line at 96 weeks indicates protocol-defined maximum duration of continuous nivolumab therapy. Gettinger at el. J Clin Oncol 2015; 33:2004-2012.

2.4 Correlative Studies Background

In a study aimed at the identification of predictive correlates of response to atezolizumab in patients with solid tumors, 277 patients with advanced cancers received atezolizumab every 3 weeks (Herbst et al. 2014). Tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1, and available pre-treatment and on treatment formalin-fixed, paraffin embedded (FFPE) tissue tumor specimens were utilized for correlative studies. Tumor cells (TC) and immune cells (IC) were stained for PD-L1 with an anti-human PD-L1 rabbit monoclonal antibody (clone SP142; Ventana, Tucson, AZ) on an automated staining platform (Benchmark; Ventana). In NSCLC patients, there was an association between response to atezolizumab and IC PD-L1 expression ($p = 0.015$), while no association was noted between TC PD-L1 expression and response to atezolizumab ($p = 0.920$). Serial on-treatment biopsies were performed in 28 patients. Regressing lesions were characterized by a dense immune infiltrate and extensive tumor cell necrosis accompanied by the apparent sterilization of cancer cells in some cases, in addition to an increase in PD-L1 expression on tumor-infiltrating immune cells and tumor cells, which was accompanied by changes in tumor IFNγ expression. In contrast, on-treatment biopsies from a subset of patients with progressive disease were characterized by lack of PD-L1 upregulation by either tumor cells or tumor infiltrating immune cells. These growing tumors were characterized by little or no tumor immune cell infiltration, presence of an intra-tumoral immune infiltrate with minimal to no expression of PD-L1 or presence of an immune infiltrate solely around the outer edge of the tumor cell mass.

PD-L1 expression levels on tumor cells and tumor-infiltrating immune cells was further evaluated as a predictive biomarker of PD-L1 benefit in the context of a phase 2 randomized controlled trial, in which patients with NSCLC who progressed on post-platinum chemotherapy were treated with either atezolizumab 1200 mg or docetaxel 75 mg/m² once every 3 weeks

(Fehrenbacher et al., 2016). Patients were stratified by PD-L1 tumor-infiltrating immune cell status, histology, and previous lines of therapy. Baseline PD-L1 expression was scored by immunohistochemistry (IHC) in tumor cells as the percentage of PD-L1-expressing tumor cells: ≥50% (TC3), ≥5% and <50% (TC2), ≥1% and <5% (TC1), and <1% (TC0), and in tumor-infiltrating immune cells as the percentage of tumor area: ≥10% (IC3), ≥5% and <10% (IC2), ≥1% and <5% (IC1), and <1% (IC0). In the intention-to-treat population, the OS was 12.6 months (95% CI 9.7–16.4) for atezolizumab versus 9.7 months (8.6–12.0) for docetaxel (HR 0.73 [95% CI 0.53–0.99]; p=0.04). Increasing improvement in overall survival was associated with increasing PD-L1 expression (TC3 or IC3 HR 0.49 [0.22–1.07; p=0.068], TC2/3 or IC2/3. HR 0.54 [0.33–0.89; p=0.014], TC1/2/3 or IC1/2/3 HR 0.59 [0.40–0.85; p=0.005], TC0 and IC0 HR 1.04 [0.62–1.75; p=0.871]), indicating the predictive benefit of PD-L1 expression.

NSCLC specimens from pre-treatment tumor samples across atezolizumab trials (n = 498) and a non-trial cohort (n = 706) were evaluated for PD-L1 expression in TC and IC using the SP142 IHC assay (Gettinger et al., 2015). TC3 or IC3, TC2/3 or IC2/3, and TC1/2/3 or IC1/2/3 tumors represented about 20%, 40% and 65% of NSCLCs, respectively. IC3 and TC3 tumors represented two distinct tumor types; IC3 tumors had a high frequency of immune infiltrates within the tumor, stroma and tumor/stroma interface, with higher expression of B- and NK-cell signatures. TC3 tumors, in contrast, were characterized by distinct histopathologic characteristics, with a dense desmoplastic and sclerotic tumor microenvironment, a lower frequency of immune infiltrates, which when present were primarily located in the surrounding stroma. Higher levels of PD-L1 promoter methylation were inversely correlated with PD-L1 expression in TC, suggesting that PD-L1 may be influenced in part by epigenetic modification. Tumors that were TC0 and IC0, representing about 35% of NSCLCs, showed little to no evidence of immune infiltration or activation, consistent with immunologic ignorance. Similar results have also been noted in a separate analysis of tumor specimens from 1,360 patients prescreened and/or enrolled in NSCLC atezolizumab trials and from 39 patients treated at Memorial Sloan Kettering Cancer Center (Kowanetz et al., 2016). Among a subset of patients with paired tumor samples, PD-L1 expression was similar across synchronous and metachronous tissues.

In addition to the PD-L1 and PD-1 expression pattern, other biomarkers for response to PD1/PD-L1 directed therapy are under investigation, including genetic mutations within cancer cells and neoantigens, cancer epigenetics and effector T cell landscape, and the microbiota (Zou et al., 2016). Utilizing whole-exome sequencing of NSCLC tumors in patients treated with pembrolizumab, higher nonsynonymous mutation burden was associated with improved objective response, durable clinical benefit, and progression-free survival (Rizvi et al., 2015). Efficacy has also been correlated with a molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations, suggesting that the genomic landscape of lung cancers is a determinant of response to anti–PD-1 therapy (Rizvi et al., 2015; McGranahan et al., 2016).

There remains much to learn of immune escape mechanisms and mechanisms of innate or acquired resistance. In mouse models of lung adenocarcinoma, mRNA sequencing of tumors progressing on anti-PD-1 therapy was associated with upregulation of alternative immune checkpoints, in particular T-cell immunoglobulin mucin-3 (TIM-3), in PD-1 antibody-bound T cells (Koyama et al., 2015). In addition, treatment with a TIM-3 blocking antibody confers a

survival advantage following failure of PD-1 blockade. In two patients who developed adaptive resistance to anti-PD-1 treatment, TIM-3 upregulation in blocking antibody-bound T cells was noted at the time of treatment failure (Koyama et al., 2015).

Collection of archival tumor specimens pre-PD-1 directed therapy (if available), mandatory biopsies at the time of enrollment and optional re-biopsy at the time of disease progression on atezolizumab, as well as mandatory collection of peripheral blood on C1D1 and optional collection of peripheral blood on day 1 of C2 through C5 will be performed for completion of translational studies aimed at identifying candidate biomarkers of response and mediators of resistance to PD-1 and PD-L1 directed therapies. The primary biomarker to be explored will be PD-L1 IHC of FFPE patient tumor specimens. Other biomarkers to be explored, based on the availability of funding, include, but are not limited to, whole exome sequencing of FFPE patient tumor specimens, sequencing of cell-free DNA (cfDNA) from plasma and immunophenotyping of PBMCs.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients with Stage IIIB/IV squamous or non-squamous NSCLC (American Joint Committee on Cancer 7th Edition Staging) who have had prior treatment with nivolumab or pembrolizumab will be enrolled in one of 3 parallel cohorts based on the following:

- Cohort 1: Patient with progressive disease on nivolumab or pembrolizumab as the BOR (defined in Section 11.1). Progressive disease must be confirmed with a confirmatory scan ≥ 4 weeks after the 1st documented date of progression.
- Cohort 2: Patients with stable disease as the BOR (defined in Section 11.1) on a minimum of 12 weeks of therapy with nivolumab or pembrolizumab.
- Cohort 3: Patients with partial or complete response as the BOR (defined in Section 11.1), followed by progressive disease, on nivolumab or pembrolizumab. A confirmatory scan at the time of disease progression must be performed ≥ 4 weeks after the 1st documented date of progression.

3.1.2 Patients must have resolution of toxic effects to Grade 1 or less from prior therapy (except alopecia).

3.1.3 Patients must sign Informed Consent Form (ICF) and show ability and willingness to comply with the requirements of the study protocol

3.1.4 Age ≥ 18 years

3.1.5 Willingness to undergo a biopsy ≤ 6 weeks of the start of study treatment to obtain formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 15 unstained slides, with an associated pathology report, for central testing of tumor PD-L1 expression

- Archival tissue is acceptable if obtained within the protocol specified period and if there is no intervening therapy between the tumor biopsy and the initiation of atezolizumab. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
- Patients who do not have tissue specimens meeting eligibility requirements will be required to undergo a biopsy during the screening period. Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
- Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

3.1.6 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 ≥ 1500 cells/μL
- WBC counts > 2500/μL
- Lymphocyte count ≥ 300/μL
- Platelet count ≥ 100,000/μL
- Hemoglobin ≥ 9.0 g/dL
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN) with the following exception:
    - Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
- AST and ALT ≤ 3.0 × ULN with the following exception:
    - Patients with liver involvement: AST and/or ALT ≤ 5 × ULN
- Alkaline phosphatase ≤ 2.5 × ULN with the following exception:
    - Patients with documented liver involvement or bone metastases: alkaline phosphatase ≤ 5 × ULN
- Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

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

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

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

3.1.9 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (Appendix A). Patients with an ECOG Performance Status of 2 will be allowed at the discretion of the Treating Investigator in agreement with the Sponsor-Investigator.

3.1.10 INR and aPTT ≤ 1.5 × 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 a stable dose.

3.2 Exclusion Criteria

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

- Hormone-replacement therapy or oral contraceptives
- Herbal therapy > 1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)
- Hormonal therapy for prostate cancer or breast cancer provided criteria in 3.2.21 are met.

3.2.2 Aes from prior anticancer therapy that have not resolved to Grade ≤ 1 except for alopecia

3.2.3 History of grade 4 immune-related adverse events requiring treatment with prednisone or history of grade 3 immune-related adverse events requiring prednisone >10 mg/kg for >12 weeks.

3.2.4 Bisphosphonate therapy for symptomatic hypercalcemia

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

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

3.2.6 Patients with acute leukemias, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma

3.2.7 Known primary central nervous system (CNS) malignancy or symptomatic CNS metastases

- Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, 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 on 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, provided treating MD believes the patient to be clinically stable to begin trial treatment.

3.2.8 Patients who are pregnant, are lactation, or breastfeeding

3.2.9 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies

3.2.10 Inability to comply with study and follow-up procedures

3.2.11 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, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.

- Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
- Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
- Rash must cover less than 10% of body surface area (BSA)
- Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
- No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.2.12 History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

- History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.2.13 Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

3.2.14 History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection

- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HbsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

3.2.15 Active tuberculosis

3.2.16 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

3.2.17 Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1

3.2.18 Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

- Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

3.2.19 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

3.2.20 Administration of a live, attenuated vaccine within 4 weeks before enrollment or anticipation that such a live attenuated vaccine will be required during the study or for 5 months after the last dose of atezolizumab

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 enrollment, at any time during the study, or for 5 months after the last dose of atezolizumab.

3.2.21 Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death or with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score ≤ 6, and prostate-specific antigen [PSA] ≤ 10 mg/mL, etc.)

3.2.22 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)

3.2.23 Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1

- Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.2.24 History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

3.2.25 Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally by the Study Coordinator.
Following registration, patients should begin protocol treatment within 5 days.
Issues that would cause treatment delays should be discussed with the Investigator. The Study Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Once the signed informed consent has been obtained, all pretreatment evaluations have been performed, and patient's eligibility has been confirmed by the coordination team and the treating physician investigator, a patient will be entered on study. To register a patient, the research nurse or data manager must complete the eligibility/registration form and review the signed Informed Consent, and HIPAA authorization form.

To complete the registration process, the research nurse or data manager will:

- Verify the eligibility
- Register the patient on study
- Assign a patient accession number

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Atezolizumab	None*	1200 mg in 250 mL NSS	IV over 60 (± 15) minutes for first	Day 1	21 days (3 weeks)

			infusion; can be increased to 30 (± 10) minutes for subsequent cycles**		

***** No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician.

The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, please see Appendix B.

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

5.2 General Concomitant Medication and Supportive Care Guidelines

Concomitant Therapy

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

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor

antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists.

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megastrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

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

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.
- Palliative radiotherapy (e.g., treatment of known bony metastases) allowed, provided it does not interfere with the assessment of tumor target lesions (e.g. the lesion being irradiated is not the only site of disease, because that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1).
- It is not a requirement to withhold atezolizumab during palliative radiotherapy.
- It is strongly recommended that:
- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity
- The use of a RANKL inhibitor (denosumab) be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab
- Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage

colony-stimulating factor, and/or pegfilgrastim) is prohibited for patients with solid malignancies.

- Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.
- Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.
- In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

5.3 Duration of Therapy

Atezolizumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator or until unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in this Section.

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 held because of Aes for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 5.4.

If a patient must be tapered off steroids used to treat Aes, atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of ≤ 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression. **Patients with radiographically confirmed disease progression may continue on study treatment if, in the opinion of the treating investigator and Sponsor-Investigator, the patient continues to benefit clinically**

from atezolizumab.

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.4 Duration of Follow Up

Patients will be followed for 12 months or until death as per standard of care after discontinuation of study therapy or until death, whichever occurs first.

The following information will be collected through chart review and/or when the subject is seen in clinic for their standard of care appointment/procedures:

- ECOG Performance Status
- CBC with Diff
- Serum Chemistry
- Concomitant Medication and Anticancer Therapy Review including radiation
- Adverse Event Review

Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

At the discretion of the sponsor-investigator the study may be closed prematurely.

5.5 Criteria for Removal from Study

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

1. Patient withdrawal of consent at any time
2. Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
3. Investigator or Sponsor determines it is in the best interest of the patient
4. Patient non-compliance, defined as not complying with treatment visits and imaging.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate Case Report Form (CRF). However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will be replaced.

Sponsor-Investigator and Genentech have the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

1. The incidence or severity of Aes in this or other studies indicates a potential health hazard to patients.
2. Patient enrollment is unsatisfactory.

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

1. Excessively slow recruitment
2. Poor protocol adherence
3. Inaccurate or incomplete data recording
4. Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
5. No study activity (i.e., all patients have completed and all obligations have been fulfilled)

6. DOSING DELAYS/DOSE MODIFICATIONS

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

The primary approach to Grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent Grade 2 irAEs 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 irAEs.

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 held because of Aes for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 5.4.

If a patient must be tapered off steroids used to treat Aes, atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of ≤ 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Sponsor-Investigator.

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.

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

Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented in this section as they have been observed in this study and are potentially immune related. See Section 5.1 for guidelines for the management of IRRs (see Appendix B for precautions for anaphylaxis).

6.1 Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of atezolizumab. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose ≤ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea. Table 1 provides a summary of dose modification guidelines for gastrointestinal toxicities.

Table 1 Dose Modification Guidelines for Gastrointestinal Toxicity

Toxicity	Description	Management
Diarrhea	Grade 2 (4–6 stools per day over baseline) < 5 days	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Investigate for etiology. Restart atezolizumab once at baseline stool frequency.
	Grade 2 (4–6 stools per day over baseline) > 5 days	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis) while etiology is being investigated. Consider referral to a gastroenterologist. Administer anti-diarrheal agent (e.g., Imodium®). Consider oral budesonide, mesalamine, or 10 mg oral prednisone equivalent per day. Restart atezolizumab once at baseline stool frequency.
	Abdominal pain Blood or mucus in stool OR Grade ≥ 3 (≥ 7 stools/day over baseline) with peritoneal signs, ileus, or fever	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Rule out bowel perforation. Consider administering prednisone 60 mg/day or equivalent. Taper steroids over 1 month. Restart atezolizumab if diarrhea is resolved and systemic steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related diarrhea or colitis.

NSAID = nonsteroidal anti-inflammatory drug.

6.2 Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of atezolizumab. While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes of increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered. Patients with LFT abnormalities should be managed according to the guidelines in Table 2.

Table 2 Dose Modification Guidelines for Hepatotoxicity

Toxicity	Description	Management
LFT abnormalities	AST/ALT (> ULN to 3 × ULN) with total bilirubin < 2 × ULN	Continue with the standard monitoring plan (i.e., LFTs every 3 weeks before dosing).
	AST/ALT (> 3 × ULN to < 10 × ULN) with total bilirubin < 2 × ULN	Continue atezolizumab. Monitor LFTs at least weekly. Consider referral to a hepatologist.
	AST/ALT > 10 × ULN	Hold atezolizumab. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day equivalent) followed by an oral prednisone (or equivalent) taper over 2–4 weeks. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart atezolizumab if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related hepatic events.

Table 2 Dose Modification Guidelines for Hepatotoxicity (cont.)

Toxicity	Description	Management
LFT abnormalities (cont.)	AST/ALT ≥ 3 × ULN with bilirubin > 2 × ULN	Hold atezolizumab. Consult a hepatologist. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day equivalent) followed by oral taper over 1 month. If LFTs results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart atezolizumab if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day.

IV = intravenous; LFT = liver function test; TNFα = tumor necrosis factor alpha; ULN = upper limit of normal.

6.3 Dermatologic Toxicity

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus irAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 3.

Table 3 Dose Modification Guidelines for Dermatologic Toxicity

Toxicity	Description	Management
Dermatologic toxicity/rash (e.g., maculopapular or purpura)	Grade 1: Mild < 10% BSA	Continue atezolizumab symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2: Moderate 10%–30% BSA	Continue atezolizumab. Consider dermatologist referral. Administer topical steroids. Consider a higher potency topical steroid if rash is unresolved.
	Grade 3: Severe	Hold atezolizumab.

	> 30% BSA	Consult dermatologist. Administer oral prednisone 10 mg or equivalent. If the rash is unresolved after 48–72 hours, administer oral prednisone 60 mg or equivalent. Restart atezolizumab if rash is resolved and systemic dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related dermatologic toxicity.

BSA = body surface area; PRN = as needed.

6.4 Endocrine Toxicity

Hypothyroidism has been associated with the administration of atezolizumab.
Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table 4.

Table 4 Dose Modification Guidelines for Endocrine Toxicity

Toxicity	Description	Management
Hypothyroidism	TSH elevated, asymptomatic	Continue atezolizumab. Start thyroid-replacement hormone, at the discretion of the treating physician.
	TSH elevated, symptomatic	Hold atezolizumab. Start thyroid-replacement hormone, at the discretion of the treating physician. Consider referral to an endocrinologist. Restart atezolizumab when symptoms are controlled by thyroid replacement and TSH levels are decreasing.

TSH = thyroid-stimulating hormone.

6.5 Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with

underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension and the following should be performed, as outlined in Table 5:

Measurement of oxygen saturation (i.e., arterial blood gas)
High-resolution CT scan of the chest
Bronchoscopy with bronchoalveolar lavage and biopsy
Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DL_{CO}])

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

Pulmonary toxicity should be managed according to the guidelines in Table 5.

Table 5 Dose Modification Guidelines for Pulmonary Toxicity

Toxicity	Description	Management
Pulmonary toxicity	GGO or non-infectious infiltrate in absence of hypoxia, or dyspnea	Hold treatment with atezolizumab. Re-evaluate after 1 week. If no worsening in GGO/infiltrates and patient still asymptomatic, resume treatment with atezolizumab. If GGO/infiltrates worsen and patient is still asymptomatic, continue to hold atezolizumab and refer for bronchoscopy. Consider starting low-dose oral prednisone 10 mg or equivalent. Re-evaluate after 1 week. Resume atezolizumab if GGO/infiltrates improving.

	Hypoxia or dyspnea in presence of GGO or infiltrate without alternative etiology	Hold atezolizumab. Consult a pulmonologist. Investigate for other etiologies and consider bronchoscopy. If bronchoscopy is consistent with immune-related etiology, start 60 mg prednisone equivalent per day followed by taper over 2 weeks. Restart atezolizumab if symptomatically improved, infiltrates are resolved, and steroid use is ≤ 10 mg prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related pulmonary events.

GGO = ground glass opacities.

6.6 Pericardial and Pleural Effusions

Pericardial and pleural involvement with associated effusions is common in patients with cancer and has the theoretical potential to be exacerbated by inflammation associated with anti-tumor immunity following PD-L1 blockade. Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with pre-existing pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions, appropriate workup includes cytology, LDH, glucose, cholesterol, protein concentrations (with pleural effusions), and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstration of hemodynamic stability, and resolution of right ventricular dysfunction.

6.7 Potential Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests.

6.8 Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy. Ocular toxicity should be managed according to the guidelines in Table 6.

Table 6 Dose Modification Guidelines for Eye Toxicity

Toxicity	Description	Management
Eye toxicity (autoimmune uveitis, iritis, or episcleritis)	Symptomatic	Hold atezolizumab. Consult ophthalmologist and start topical corticosteroid eye drops. Atezolizumab may be restarted following resolution of the events. Permanently discontinue atezolizumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

7. REPORTING OF SERIOUS ADVERSE EVENTS

7.1 Adverse Event Definitions

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Suspected adverse reaction. Any adverse event for which there is a reasonable possibility that the drug caused the adverse event (considered "possibly related"). For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of suspected adverse reactions where there is reason to conclude that the drug caused the event.

Serious Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Specifically, results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Any subject death within 30 days of the last dose of study drug, regardless of the causality or a secondary malignancy should also be recorded as a serious adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator), its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan or clinical protocol; or is not

listed at the specificity or severity that has been previously observed and/or specified. If an investigator brochure is not required or available, suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure can also be considered unexpected. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s). All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0.

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Principal Investigator.

In the event of an adverse event the first concern will be for the safety of the subject.

Review of safety information. The principal investigator / sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

7.2 Assessment of Adverse Events

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

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

Yes

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

No

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

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

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

7.3 Documentation of Serious Adverse Events

In the event of a serious adverse event, the PI, the institutional review board (per institutional reporting requirements), and Genentech will be notified using the internal CRS departmental SAE form.

All events meeting the definition of a serious adverse event should be recorded on the CRS internal departmental SAE form and submitted to

1. PI: Liza Villaruz, MD
    a. Phone: 412-648-6577
    b. Fax: 412-648-6579
    c. Email: villaruzl@upmc.edu
2. CRM: Jennifer Ruth
    a. Phone: 412-623-8963
    b. Fax: *412- 623-7862*
    c. Email: ruthj2@upmc.edu
3. CRSSafetySubmissions@upmc.edu
4. Local Institutional Review Board per institutional reporting requirements
5. Genentech: (Using Appendix C Fax Coversheet)
   Fax: 650-238-6067 or Email: usds_aereporting-d@gene.com

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Narrative (Section C) on the CRS internal departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known

The adverse event severity grading scale for the NCI CTCAE (v4) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

Follow-up reports:

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

7.3 Methods and Timing for Assessing and Recording Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

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

7.3.1 Adverse Event Reporting Period

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

7.3.2 Genentech Specific Instructions for Recording Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:
- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

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

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

7.3.2.1 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 7.3.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

7.3.2.2 Pre-existing Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-

assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

7.3.2.3 Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

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

7.3.2.4 Pregnancies in Female Patients

If a female subject or female partner of a male study subject becomes pregnant while receiving atezolizumab or within 5 months after the last dose of atezolizumab, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the atezolizumab should be reported as an SAE.

7.3.2.5 Post-Study Adverse Events

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

7.3.3 Safety Reconciliation

The Sponsor agrees to conduct reconciliation to ensure that all single case reports have been adequately received by Genentech via the Sponsor emailing Genentech a quarterly line-listing documenting single case reports sent by Sponsor to Genentech in the preceding time period

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

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

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

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

7.3.4 Adverse Events of Special Interest

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

Non Drug Specific Adverse Events of Special Interest:

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
  - Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

Adverse Events of Special Interest for Atezolizumab:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, macrophage activating syndrome and hemophagocytic lymphohistiocytosis.
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

7.4 Reporting of Suspected Adverse Reactions to Genentech

Exchange OF SINGLE CASE REPORTS

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

Investigators must report all the above mentioned single case reports adequately to Genentech within the timelines described below. The completed Genentech approved reporting forms (internal CRS departmental SAE form) should be faxed immediately upon completion to Genentech Drug Safety using fax cover sheet (appendix C) at:

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

[redacted]

[redacted]
and Product Complaints (with or without an AE) originating from the study.

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

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), Product Complaints (with or without an AE)and other Special Situation Reports where the patient has been exposed to the Genentech Product, will be sent on Genentech approved reporting forms (CRS Departmental SAE Forms) to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

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

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

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

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

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

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

- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population
-

Product Complaints

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

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

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.

It is understood and agreed that the Sponsor will perform adequate due diligence with regard to obtaining follow-up information on incomplete AE, Special Situations and pregnancy reports.

7.5 Reporting to Regulatory Authorities, Ethics Committees and Investigators

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

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

Additional Reporting Requirements for IND Holders:

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

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

7 Calendar Day Telephone or Fax Report:

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

15 Calendar Day Written Report

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

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

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

FDA fax number for IND Safety Reports:

[redacted]

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

[redacted]

And Sponsor will be responsible for the distribution of safety information to Site IRB (Section 7.10)

Reports will be submitted to the University of Pittsburgh IRB throught the PittPro online application system. at www.pittpro.pitt.edu.

[redacted]

[redacted]

7.6 Aggregate Reports

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

[redacted]

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

7.7 Study Close Out

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

[redacted]

7.8 Queries

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

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

7.9 Safety Crisis Management

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

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

7.10 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after

the determination was made.

8. PHARMACEUTICAL INFORMATION

8.1 Atezolizumab

Mode of Action: Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution that results in a non-glycosylated heavy chain that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007). Therapeutic blockade of PD-L1 by atezolizumab is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, resulting in improved anti-tumor activity.

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

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

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

Route of Administration: Intravenous (IV) infusion.

Method of Administration: The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [± 2] days). Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

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

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

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix B.

Potential Drug Interactions: Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 Archival and Fresh Tumor Tissue Samples for Screening

If available, archival specimens prior to PD-1 directed therapy with nivolumab or pembrolizumab must be collected. Mandatory biopsies at the time of enrollment will be performed ≤ 6 weeks prior to study treatment initiation. Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, must be submitted at screening for determination of PD-L1 status by IHC utilizing the SP142 antibody (Ventana, Tucson, AZ). Additional exploratory biomarkers may be evaluated, based on the availability of rationale and funding.

- Archival tissue is acceptable if obtained within the protocol specified period (≤6 weeks prior to the initiation of atezolizumab) and if there is no intervening therapy between the tumor biopsy and the initiation of study treatment. Tumor tissue should be of good quality based on total and viable tumor content. Fine needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.
- Patients who do not have tissue specimens meeting eligibility requirements will be required to undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum of three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
- Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

9.1.2 Tumor Samples at the Time of Radiographic Progression

Patients who are treated with atezolizumab may undergo an optional tumor biopsy to obtain a tumor sample ≤ 4 weeks from the date of disease progression. Determination of PD-L1 status at the time of progression and additional exploratory biomarkers may be evaluated, based on the availability of rationale and funding.

Acceptable samples include:

- Core needle biopsies for deep tumor tissue; at least three cores, embedded into a single paraffin block, should be submitted for evaluation.
- Excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous or mucosal lesions
- Tumor tissue resection

9.1.3 Tumor Samples at Other Time Points

If a patient undergoes a medically indicated procedure (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) 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 (leftover tumor tissue) may be obtained for exploratory analysis. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and implications for immune checkpoint blockade.

9.1.4 Blood collection

Additional studies may be performed on peripheral blood in order to understand mechanisms of immune escape and assess biomarkers of response. These studies may include but are not limited to whole exome sequencing. In order to facilitate these studies, blood will be collected at the following time points:

Venous blood will be collected prior to treatment on C1D1 (mandatory). Optional venous blood will be collected on C2D1, C3D1, C4D1, and C5D1.

9.1.4.1 Sample Collection in EDTA tubes:

Separate plasma and PBMCs from whole blood at collection site:

- Collect two10ml purple top EDTA tubes per collection time point.
- Fill each of the two 10 ml EDTA tubes completely with whole blood.
- Mix each EDTA tube thoroughly by slowly inverting the collection tube at least 10 times.
- Plasma and PBMC isolations as per lab protocol with cell count.
- Ensure to label tubes sufficiently:
  - Subject ID
  - Gender
  - Specimen type (plasma or PBMC)
  - Specimen collection date

An additional 3 ml of whole blood will also be collected for germline DNA isolation to be used as normal control for whole exome sequencing:

- Collect 3 ml blood in one 6ml K3EDTA purple top tube at C1D1.
- Mix the tube thoroughly by slowly inverting the collection tube at least 10 times.
- Ensure to label tubes sufficiently:
  - Subject ID
  - Specimen type (whole blood/ WB)
  - Specimen collection date and time
  - The samples will be shipped on date of collection to Genentech Designated Vendor from collection site

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1			Cycle 2			Subsequent Cycles			Off Treatment[k]
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	
Atezolizumab		X			X			X			
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X									X
Physical exam	X	X			X			X			X
Vital signs[a]	X	X			X			X			X
Height	X										
Weight	X	X			X			X			X
Performance status[b]	X	X			X			X			X
CBC w/diff, plts[c]	X	X			X			X			X
Serum chemistry[d]	X	X			X			X			X
Coagulation[e]	X	X			X			X			X
Urine β-HCG[f]	X										
Urinalysis[g]	X	X			X			X			X
Thyroid function testing[h]	X	X			X			X			X
Amylase and Lipase	X	X			X			X			X
Viral Serologies[i]	X										
Biomarker Analysis and DNA sequencing		X[n]			X[o]			X[o]			
Adverse event evaluation	X	X----------X									X
Tumor measurements	X	X----------X									
Radiologic evaluation[j]	X	X----------X									

Tumor Biopsy[l]	X										X (optional)
Archival tissue pre-PD1 therapy, if available[l]	X										
Peripheral Blood Sample Collection[m]		X[n]			X[o]			X[o]			

[a] Heart rate, respiratory rate, systolic and diastolic blood pressure 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.

[b] Appendix A.

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

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

[e] aPTT and INR

[f] For women of childbearing potential and who are premenopausal. To be performed at screening and otherwise, if clinically indicated.

[g] Specific gravity, pH, glucose, protein, ketones, and blood.

[h] TSH, free T3, free T4

[i] Epstein-Barr virus (EBV) serology (EBNA IgG), hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV)

[j] Radiographic evaluations must be performed every 6 weeks ± 1 weeks. Confirmatory scans will also be obtained ≥4 weeks following initial documentation of an objective response or progressive disease.

[k] Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

[l] Baseline archival tissue is acceptable if obtained within the protocol specified period (≤6 weeks prior to the initiation of atezolizumab) and if there is no intervening therapy between the tumor biopsy and the initiation of study treatment. Additional details regarding submission of baseline tumor specimens and archival pre-PD-1 tumor tissues are provided in Section 3.1.5 and Section 9.

[m] Additional details regarding sample collection are provided in Section 9.

[n] Mandatory.

[o] Optional, through C5D1.

Note: There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the treating investigator, and as discussed with the Sponsor-Investigator if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-UPMC insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family

emergencies, etc.).

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks ±1 week. In addition to a baseline scan, confirmatory scans should be obtained ≥ 4 weeks following initial documentation of objective response or progressive disease.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with atezolizumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable after discussion with the Sponsor-Investigator.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in 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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as 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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. 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 diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize

each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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 in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at

CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of 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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-	No	PR	≥4 wks. Confirmation

	PD			
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: 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 "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Data Safety Monitoring Plan

Sponsor-Investigator, Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the DSMB meetings are available to anyone unable to attend the center DSMB.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the HCC DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the HCC DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

12.2 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and Guidelines on Good Clinical Practice compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator (i.e., the study site principal investigator) and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

12.3 Data Handling and Record-Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in accordance with Good Clinical Practice.

The investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

12.4 Institutional Review Board (IRB) Approval

The investigator (i.e., the study site principal investigator) will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on

Harmonization (ICH) Guidelines on Good Clinical Practice.

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an sponsor's decision to modify the previously accepted clinical protocol, the sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or AE; or the dropping of a test intended to monitor the safety of the investigational drug.

12.5 Ethical and Scientific Conduct of the Clinical Study

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and University of Pittsburgh Medical Center, Commonwealth of Pennsylvania, and applicable federal agencies.

12.6 Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the sponsor, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of

enrolled subjects for continued participation in the clinical study.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

For each of the 3 cohorts, Simon's optimal two-stage design is used to minimize the expected sample size if the treatment is not effective. The primary endpoint is best overall response (BOR) by RECIST 1.1 (Complete Response or Partial Response, vs. Stable Disease or Progressive Disease). Patients who are lost to follow-up without achieving CR or PR are considered non-responders for the primary analysis, with the exception of patients who withdraw from the study before C2D1 for reasons explicitly unrelated to disease or toxicity. (Occasionally a patient may withdraw because of insurance concerns or to avoid additional travel required to receive study treatment.)

Progression-free survival (PFS) is measured in months from start of treatment to time of progression or death, with date of progression the date of first radiographic evidence of progression that is later confirmed as PD (rather than pseudo-progression). If progression or death is not observed on study, PFS is censored at the date of last radiographic assessment without PD. If the first evidence of PD is from a radiographic assessment that is ≥12 weeks overdue, PFS is censored at the date of last radiographic assessment without PD.

Duration of response is measured as time in months from CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (using the same criteria for PD as for PFS with respect to timing and censoring)

Overall survival (OS) is measured as months from first study treatment until death or last contact confirming that the patient is alive.

13.2 Sample Size

For each cohort, a BOR rate of 15% would be promising compared to a null rate of 2%. The target enrollment is 37 evaluable patients within each cohort. A stopping rule for futility is implemented if none of the first 11 evaluable patients within a cohort have a confirmed objective response. Accrual may continue during follow-up for these patients. If 1 or more responses are observed in the first 11 evaluable patients in a cohort, an additional 26 patients will be enrolled. Importantly, if one cohort meets criteria for futility in stage 1, the other cohort(s) may proceed to stage 2, if indicated. A promising study result would be if 3 or more responses are seen at the conclusion of stage 2. This design has 80% power for each cohort to detect a true response rate of 15% (compared with a null rate of 2%). The one-sided type 1 error rate is 0.05 for each cohort.

Thus, the minimum sample size is 33 for the study (3 cohorts), and the maximum sample size is 111.

13.3 Analysis cohorts

All enrolled patients who receive at least one dose of study therapy will be included in primary assessments of both efficacy and safety, with the exception of patients not evaluable for the primary analysis (see 13.1). Secondary analyses may examine subsets of patients based on the delivered dose of therapy.

13.4 Analysis plans

13.4.1 Primary objective

Futility stopping rules for the Simon optimal two-stage design are described above (Section 13.2). A promising study result is 3 or more responses (PR or CR as BOR) in 37 patients. For each cohort, the overall response rate (ORR) for best overall response and 90% and 95% confidence intervals will be estimated using a uniformly minimum variance unbiased estimator appropriate for a two-stage trial (Jung et al, 2004 and Jung, 2015).

13.4.2 Secondary objectives

For patients experiencing complete or partial tumor responses, the distribution of response duration will be characterized by the median and quartiles, , and graphical display of Kaplan-Meier estimates of response duration, separately for each cohort and for all responders.

Progression-free survival (PFS, months from start of treatment to time of progression, death or last radiographic assessment without PD, whichever occurs first) and overall survival (OS, months from first study treatment to death or last contact) will be summarized separately for each cohort. The PFS function and median PFS will be estimated by the Kaplan-Meier method, with a 90% confidence interval using the Greenwood variance formula applied to log-transformed survival.

Adverse events will be graded using the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) version 4. Adverse events of grade 3 or greater determined to be possibly, probably or definitely related to treatment, or that result in dose holds or reductions, will be collected and reported. Adverse events and serious adverse events will be tabulated in order of prevalence, with the highest grade reported by each patient. The number and percent of subjects reporting adverse events will be summarized by category (i.e., “Blood and lymphatic system disorders”), for the most common adverse event subcategories (i.e., “anemia”), and for serious adverse events (defined in section 7.2). Narratives of all serious adverse events and deaths on-study will be provided. All safety data will be tabulated separately by cohort, and for the full study sample.

13.4.3 Exploratory objectives

PD-L1 expression will be measured in tissue from a mandatory biopsy conducted after discontinuation of the prior therapy and before initiation of study therapy. The primary analysis

will examine associations between PD-L1 expression and best overall response by RECIST 1.1, for all cohorts combined. These two ordinal variables (immunohistochemistry and response) will first be described graphically in a mosaic plot, which may suggest a clinically relevant dichotomization of PD-L1 expression and/or best overall response. Further analysis may use generalized linear model approaches for ordinal regression, or treat response as dichotomous or continuous, with limited models fit to avoid "p-hacking".

REFERENCES

Borghaei H., Paz-Ares L, Horn L., et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Eng J Med 2015; 373:1627-39. DOI: 10.1056/NEJMoa1507643.

Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010; 28: 3167-75.

Brahmer JR, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Eng J Med 2015; 373:123-35. DOI:10.1056/NEJMoa1504627.

Chen YB, Mu CY, Huang JA. Clinical significance of programmed death-1 ligand-1 expression in patients with non-small cell lung cancer; a 5-year follow-up study. Tumori 2012; 94:107-16.

Ettinger DS, Akerley W, Bepler G, Blum MG, Chang A, Cheney RT, et al. Non-small cell lung cancer. J Natl Compr Canc Netw 2010;8:740-801.

The Federal Drug Administration. FDA approves Keytruda for advanced non-small cell lung Cancer. October 2nd, 2015.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465444.htm

Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837-46.

Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus doctaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomized controlled trial. Lancet Oncol 2013; 14:981-8.

Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. N Eng J Med 2015; 372: 2018-2028.

Garon, EB. Current Perspectives in Immunotherapy for Non-Small Cell Lung Cancer. Seminars in Oncology 2015; 42 (suppl 2): s11-s18.

Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015; 33: 2004-12.

Gettinger SN, Kowanetz M, Koeppen H, Wistuba II, Kockx M, Kadel EE, Rizvi NA, Spira AI, Hirsch FR, Boyd Z, Denker M, Minn A, Shames DS, Sandler A, Chen DS, Hegde PS, Spigel DR; Yale School of Medicine, New Haven, CT; Genentech, Inc., South San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Histogenex, Berchem,

Belgium; Columbia University Medical Center, New York, NY; Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax, VA; University of Colorado Cancer Center, Denver, CO; Sarah Cannon Research Institute, Nashville, TN. Molecular, immune and histopathological characterization of NSCLC based on PDL1 expression on tumor and immune cells and association with response to the anti-PDL1 antibody MPDL3280A. J Clin Oncol 33, 2015 (suppl; abstr 3015).

Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22:1589-97.

Herbst RS, Baas P., Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. The Lancet. Epub December 18th 2015; DOI: 10.1016/s0140-6736(15)01281-7

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7. doi: 10.1038/nature14011.

Horn L, Spiegel D, Gettinger S. Clinical activity, safety and predictive biomarkers of the engineered antibody atezolizumab (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study. J Clin Oncol 2015; 33 (suppl; abstr 8029).

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D**.** Global cancer statistics. CA Cancer J Clin 2011;61:69-90.

Jung SH. Statistical issues for design and analysis of single-arm multi-stage phase II cancer clinical trials. Contemp Clin Trials. 2015 May;42:9-17.

Jung SH, Kim KM. On the estimation of the binomial probability in multistage clinical trials. Stat Med. 2004 Mar 30;23(6):881-96.

Kowanetz, Marcin, et al. "Abstract A017: PD-L1 as a predictive biomarker for atezolizumab (MPDL3280A; anti-PDL1) in non-small cell lung cancer (NSCLC)." Cancer Immunology Research 4.1 Supplement (2016): A017-A017.

Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, Richards WG, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016 Feb 17;7:10501.

Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba, II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311:1998-2006.

McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016 Mar 25;351(6280):1463-9.

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12:252-64.

Rizvi NA, Brahmer JR, Ou S-HI, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33 (suppl; abstr 8032).

Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.

Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18:2095-103.

Somasundaram A, Socinski MA, Burns TF. Personalized treatment of EGFR mutant and ALK-positive patients in NSCLC. Expert Opin Pharmacother 2014;15:2693-708.

Spira AI, Park K, Mazieres, J. et al. Efficacy, safety and predictive biomarkers results from a randomized phase II study comparing PDL3280A vs docetaxel in 2L/3L NSCLC (POPLAR). J Clin Oncol 2015; 33 (suppl; abstr 8010).

Sui X, Ma J, Han W, et al. The anticancer immune response of anti-PD-1/PD-L1 and the genetic determinants of response to anti-PD-1/PD-L1 antibodies in cancer patients. Oncotarget 2015; 6: 19393–19404.

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

Velcheti V, Schalper KA, Carvajal DE, et al. Programmed death ligand-1 expression in non-small cell lung cancer. Lab Invest 2014; 94:107-16.

Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med. 2016 Mar 2;8(328):328rv4.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B ANAPHYLAXIS PRECAUTIONS

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Genentech
A Member of the Roche Group

APPENDIX C SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

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

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

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

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

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET